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J952-50

QUALITY AND RELEVANCE OF RESEARCH AND RELATED ACTIVITIES AT THE GORGAS MEMORIAL LABORATORY

A TECHNICAL MEMORANDUM

AUGUST 1983

Technical Memoranda are issued by OTA on specific subjects analyzed in recent OTA reports or on projects presently in process at OTA. They are issued at the request of Members of Congress who are engaged in committee legislative actions which are expected to be resolved before OTA completes its assessment.

CONGRESS OF THE UNITED STATES
Office of Technology Assessment
Washington, D. C. 20510

Recommended Citation:

Quality and Relevance of Research and Related Activities at the Gorgas Memorial Laboratory—A Technical Memorandum (Washington, D.C.: U.S. Congress, Office of Technology Assessment, OTA-TM-H-18, August 1983).

Library of Congress Catalog Card Number 83-600577

For sale by the Superintendent of Documents,
U.S. Government Printing Office, Washington, D.C. 20402

Foreword

The Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc. (GMI) and its operating arm, the Gorgas Memorial Laboratory (GML) have been conducting tropical research, training, and public health activities for more than half a century. Questions about GMI's continued existence were raised this spring when the National Institutes of Health requested no funds for the core support for GML. Gorgas' existence is at stake because the core support appropriation by the United States represents about three-quarters of GMI's total budget.

The Senate Committee on Appropriations and its Subcommittee on Labor, Health and Human Services, and Education requested that the Office of Technology Assessment (OTA) examine the quality and relevance of research and related activities of GML. Such information is needed in order to adequately judge whether the core support should be terminated. The subcommittee also requested that the General Accounting Office undertake a concurrent evaluation of four areas: the peer review process at GMI/GML, the extent of other federally funded tropical medicine research activities, efforts by Gorgas to broaden its financial base of support, and the possible impacts on U.S. regional relationships if funding was terminated.

This technical memorandum presents the results of OTA's examination. It reviews the quality and relevance of activities at GML, based on Gorgas' publishing record, an OTA-commissioned survey of GML's scientific reputation, a critical review of recent articles and current manuscripts, a comparison of GML's areas of effort with health problems in tropical America and with scientific opportunity, and a review of past scientific evaluations of GML.

OTA finds that GML's research and related activities are generally of high quality and relevance to the region and the United States. The United States receives excellent benefit for its contribution to GMI/GML. If Gorgas were to close down, the United States would most likely have to develop a capability to undertake many of the current activities of GML. OTA finds that there would be both health-related and international relations repercussions if the United States were to withdraw its support for GML. Although GMI could be improved in several significant respects, GML is producing important work of high quality and represents an excellent investment of health funds.

This memorandum benefited from the consultation and review of a large number of persons in the Federal Government, universities, international health organizations, and private industry. Key OTA staff involved in the analysis and writing were Hellen Gelband, Clyde J. Behney, Steven S. Bjorge, and John S. Willems.

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Chapter 1

Introduction and Background

Chapter 1

Introduction and Background

The Gorgas Memorial Laboratory (GML) is a research institution concerned with tropical medicine and public health. It undertakes both applied and basic research, and performs laboratory, clinical, and field research activities. GML was established in 1928 in commemoration of the work of Gen. William Gorgas in in controlling yellow fever. The Laboratory is located in Panama City, Republic of Panama. It is the research arm of the Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc. (GMI), a (U.S.) domestic, nonprofit corporation headquartered in Washington, D.C.

This technical memorandum presents the results of a review of the quality and relevance of research and related activities of GML. The evaluation was conducted at the request of the Senate Committee on Appropriations and, especially, its Subcommittee on Labor, Health and Human Services, and Education. It is part of a broader OTA assessment of the status of biomedical research and related technology for tropical medicine, also requested by the committee and subcommittee.

INTRODUCTION

GML is a specific subject of evaluation because of questions concerning its fiscal year 1984 appropriation. GMI is authorized by act of Congress (Public Law 70-350, as amended) to receive a yearly appropriation, not to exceed $2 million, from the U.S Government. The original fiscal year 1984 budget request from the Fogarty International Center (FIC)—the unit of the National Institutes of Health (NIH) given responsibility for administering the Gorgas budget request—included a budget request for Gorgas. A subsequent revision by NIH, of the NIH budget, led NIH/FIC to request no funds at all for core support of GMI. Because this core support of close to $2 million is an extremely large percentage of the total GML budget (see ch. 2), this action effectively meant that GML would have to close down.

In order to evaluate whether this action was justified on the basis of the quality of Gorgas' research and on its success in identifying needs and conducting research relevant to health concerns of Panama and tropical America* (especially Central America and the Caribbean), the requesting subcommittee and committee asked both the General Accounting Office (GAO) and the Office of Technology Assessment (OTA) to provide relevant information.

The related effort by GAO examines four topics:

1. the process of peer review used by GML before initiating research projects and after their completion,
2. efforts to broaden the financial base of GML,
3. other federally funded tropical medicine research activities, and
4. the possible impact of GML's closing on U.S.-Panamanian relations. That report is scheduled for completion in August 1983.

The OTA effort devotes some attention to the first of those four topics, but is primarily addressed to issues of:

1. the quality of GML's applied biomedical research projects, epidemiological activities, maintenance of research animal populations, and other research-related activities such as training; and
2. the relevance of GML's research and other activities to the health needs and problems of Panama, other tropical American countries, the U.S. interests, and to tropical medicine in general.

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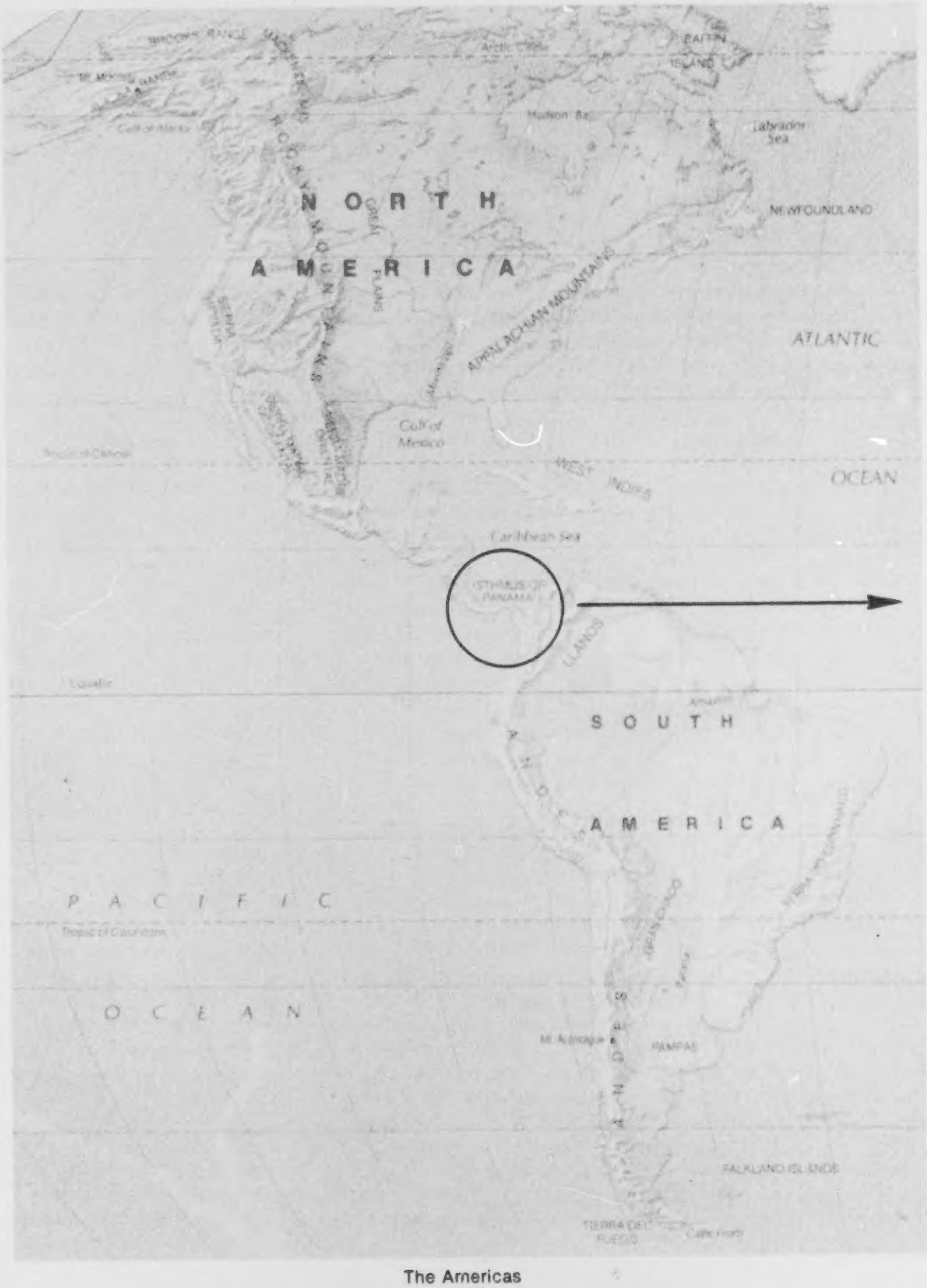
*The term tropical America here refers to the southern part of North America, all of Central America and the Caribbean, and tropical South America.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SIERRA NEVADA
ATLANTIC
OCEAN
Gulf of Mexico
Tropic of Cancer
WEST INDIES
Caribbean Sea
ISTHMUS OF PANAMA
LLANOS
Equator
Amazon
SOUTH AMERICA
ANDES
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The Americas

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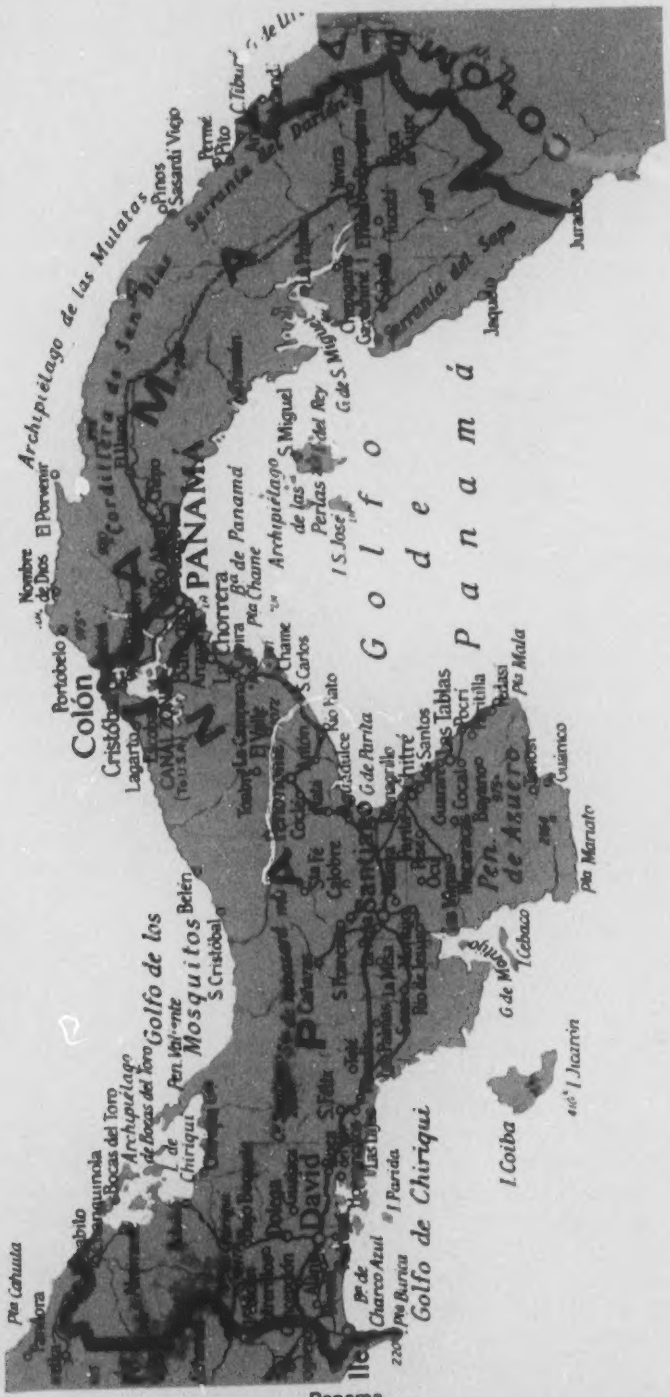
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PANAMÁ
CANAL ZONE (To U.S.A.)
La Chorrera
Archipielago de las Perlas
S. Miguel
I. S. José
Golfo de Panamá
G. de S. Miguel
La Palma
Yaviza
Jaqué
Puerto Piña
Pinos
Sasardí Viejo
Permé
Pto. Pito
C. Tiburón
Golfo de los Mosquitos
Belén
S. Cristóbal
Pen. Valiente
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Bocas del Toro
Laguna de Chiriquí
David
Golfo de Chiriquí
I. Parida
Br. de Charco Azul
Pta. Burica
Pta. Cotuala
I. Coiba
I. Jicarón
I. Cébaco
G. de Montijo
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Pen. de Azuero
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S. Carlos
Chame
Pta. Chame
Ba. de Panamá
Ba. de Chame
G. de Parita
El Valle
Santa Fé
Calobre
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Las Palmas
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Pocrí
Jurado
Lagarto
El Llano
Chepo
Garachiné
Chepigana
Punta Alegre

Panama

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Organization of the Technical Memorandum

The remainder of this chapter contains a summary of the findings and conclusions of the technical memorandum and background information on the Tropics, tropical diseases, and the role of research laboratories located in the Tropics. Chapter 2 presents descriptive material on Gorgas, its structure, and past and current research activities. Chapter 3 examines evidence on the quality of GML's research, public health, and training activities.

The fourth chapter presents descriptions and brief data on the status of the diseases and health problems of critical importance to tropical America and of research related to them. Gorgas's activities are then discussed in the context of these diseases and conditions. The final chapter presents the findings and conclusions.

Appendix A presents the acknowledgments, lists the members of the Liaison Group formed by the Pan American Health Organization to provide advice to OTA on this project, and lists the OTA Health Program Advisory Committee. Appendix B is a brief presentation of other current research activities in tropical health. Appendix C is a bibliography of publications since 1975 by GML staff. Appendix D is a summary of the OTA survey of experts' opinions concerning Gorgas and its research quality and relevance. Appendix E contains a list of acronyms and a glossary of terms.

SUMMARY OF FINDINGS AND CONCLUSIONS

OTA examined the quality and relevance of tropical medicine research and related activities at GML. The evaluation of the quality of an institution such as Gorgas cannot take place without explicit recognition of certain premises:

- There is an inherent value in supporting tropical research laboratories in tropical countries. Field conditions present opportunities that cannot be duplicated by organizations such as NIH.
- Evaluations of the *quality* of research are inevitably, and properly, made partly on the basis of fairly objective criteria such as publications record and partly on the basis of subjective judgments by qualified individuals.
- The criteria used to judge quality, although similar in type, need to be modified and weighted differently for research performed in well-equipped, state-of-the-art laboratories than for field research laboratories.
- Relevance is directly dependent on the type and location of institution, and it should be examined from each of the appropriate viewpoints (e.g., host country, region, United States, general advancement of knowledge).

With these premises in mind, OTA examined the quality of Gorgas' research against a range of objective and subjective criteria. There was very impressive agreement among the results of: 1) the past scientific evaluations of GML, 2) the critical evaluation of the research design and presentation of articles and manuscripts, 3) the survey of expert scientific opinion on Gorgas' quality, 4) interviews with Panamanian health officials and professionals, 5) the examination of GML staff's publications record, and 6) an examination of GML's record of competing for grants and contracts. All evidence gathered by OTA led to the finding that **the overall scientific quality of GML is high, especially when considered in the context of GML's status as a research laboratory located in the Tropics.** Quality was, naturally, not uniformly even.

OTA also found that the large majority of GML's research is highly or adequately relevant to health concerns and problems of Panama, the tropical American region, U.S. interests, and the advancement of scientific knowledge and the field of tropical medicine in general. (Table 1 lists significant accomplishments of GML in the past decade; table 2 shows significant activities during the previous period of GML's history.) The evidence for this finding lies, for the first two, in the match between tropical health problems and GML research directed at them, and from strongly

Table 1.—The Gorgas Memorial Laboratory's Major Accomplishments From 1970 to the Present

- Continued yellow fever surveillance and monitoring of vectors
- St. Louis encephalitis and Venezuelan equine encephalitis vectors and reservoirs
- Insect genetic studies using isozyme markers
- Transovarial transmission of yellow fever virus in mosquitoes
- Use of *Aotus* monkey model for testing of therapeutics
- Several new viral isolates in area
- Screening of antimalarial drugs and identification of promising therapeutic antimalarial compounds
- WHO regional center for bloodmeal analysis
- Improved identification of insect vectors: sandflies, triatomines, blackflies, etc.
- Development of cancer registry in the Republic of Panama
- Discovery of high incidence of cervical and penile cancer in Herrera Province (Republic of Panama)
- Studies of sexually transmitted diseases in the Republic of Panama (the first such studies in Latin America)
- Rapid identification of viral agent in recent epidemics of conjunctivitis and encephalitis in the Republic of Panama
- Discovery of high HTLV antibodies in the Republic of Panama
- Environmental impact assessment of Tabasara Hydroelectric project

SOURCE: Gorgas Memorial Laboratory, Office of the Director, August, 1983.

expressed opinions and examples by various Panamanian officials and professionals.

The importance of GML to Panama cannot be judged solely on the basis of Panama's monetary contribution. Panama is going through a difficult economic period. Even so, the Ministry of Health has arranged a loan to keep GML in operation for the remainder of fiscal year 1983. The value of the land, buildings, and tax-favored status have never been adequately assessed. And to put the often criticized direct financial contribution of $10,000 from Panama in perspective, the research budget of the Panamanian medical school is reportedly only $20,000. As one official of the U.S. Department of State expresses it: Each year, the United States sends a message to Panama and the region by funding GML and supporting activities related to the health of U.S. and Panamanian citizens alike (51).

Activities related to the recent Panama Canal Treaty process provide a specific example of the importance of GML to Panama. As part of the treaty, a Joint Committee on the Environment was established. Panama turned to GML, as the only institution in Panama with the necessary skills and experience, for assistance in relation to environmental protection and human and animal health, and additionally named Dr. Pedro Galindo, formerly of GML, as the senior Panamanian on the Committee.

Relevance to U.S. health interests can be found in the surveillance activities, the training activities, and the various research activities undertaken under contract to the U.S. military. There are about 20,000 U.S. Government employees and dependents in Panama; and many thousands more in nearby countries. The work of GML is directly relevant to the health of these people.

Gorgas's contributions in the areas of malaria, yellow fever, and leishmaniasis illustrate its relevance to the general advancement of knowledge (see also, tables 1 and 2).

Based on the above evidence, OTA finds that **with some exceptions that occur almost entirely within the core-funded activities, the research conducted at Gorgas is relevant to the various parties at interest.**

Conclusions: OTA concludes that the benefits of supporting GML justify, on scientific and other grounds, the relatively small amount of funds required. Quality and relevance are high. Withdrawing core support from Gorgas would probably not even save the amount of the appropriation, since other Federal agencies may need to either conduct or support research now carried out at GML.

Gorgas is not ideal; improvements could certainly be made. Some of the shortcomings stem from its uncertain funding. The prospect of unstable funding and perhaps closure may have kept individual scientists from joining GML or becoming visiting scientists there and may reduce the desire of U.S. universities to collaborate with GML on research projects.

Another example of the effect of uncertain funding has been the decision by the U.S. Navy to hold off on the next scheduled training class, because the course would extend a few weeks into fiscal year 1984. It is extraordinarily difficult to

Table 2.—Major Accomplishments of the Gorgas Memorial Laboratory, 1929-69

I. Protozoal Diseases of Man and Lower Animals:

Malaria:

1933 and subsequently: First long-range, large-scale field tests of the antimalarial drugs, Atebrine, chloroquine, and paludrine under controlled conditions in the New World Tropics.

1954: First long-range field tests of DDT house-spraying to control malaria.

1960: Field demonstration of the effectiveness of weekly doses of pyrimethamine-primaquine drugs combined with the eradication of *Plasmodium falciparum* malaria from a tropical area.

1966: Demonstration that certain common human malaria parasites could be grown in certain species of Panamanian monkeys and could be transferred to man and other monkeys by blood inoculation and by bites of mosquitoes.

American Trypanosomiasis:

1931: First report of Chagas' disease in Panama and discovery of the vectors.

1959: First report of *Trypanosoma rangeli* from man and wild vertebrates in Panama and demonstration of the development of the human strain in the salivary glands of *Rhodnius pallescens.*

1965: Demonstration that the Panamanian strain of *T. rangeli* differs from the South and Central American strains in its behavior of development in the insect vector.

Leishmaniasis:

1965: Incrimination of seven wild vertebrates as reservoir hosts of human leishmaniasis.

1966: Demonstration that leishhmania infection may commonly occur in the apparently normal skin of some feral animals without producing lesions.

1945-68: Recognition of over 70 species of *Phlebotomus* in Panama, of which 4 or 5 have been found infected with leishmania.

Animal Trypanosomiasis:

1932: Discovery of the vampire bat transmission of equine trypanosomiasis.

1932: Discovery of bovine trypanosomiasis in Panama.

Intestinal Protozoa:

1944: First finding of *Isopora hominis* in Panama.

II. Helminthic Diseases of Man and Lower Animals:

1934-35: First comprehensive survey of the worm parasites of equines in Panama.

1966: Finding a new human disease entity caused by *Echinococcus oligarthrus*, a little known cestode parasite of pumas and other large felines; description of the first known human case that terminated fatally; and demonstration of the life cycle of the parasite.

III. Rickettsial Diseases:

1946: First report of Q Fever in Panama.

1947: First report of murine typhus in Panama.

1951: First recognition of Rocky Mountain Spotted Fever in Panama.

IV. Virus Diseases:

1949: First demonstration of the mosquito vectors of yellow fever in Panama and Central America and the inauguration of comprehensive studies on vector ecology and transmission capabilities.

1957: First recovery of St. Louis encephalitis virus and recognition of human cases in Panama.

1958: First isolation of Ilheus virus in Central America.

1960: First isolation of Changuinola virus from man.

1961: Discovery of four new arboviruses: Madrid, Ossa, Patios, and Zegla.

1963: First isolation of Wyeomyia subgroup of arboviruses from man.

1964: Recognition of the first human case of Ilheus encephalitis.

1965: Finding of crab-hole mosquitoes *(Deinocerites)* as hosts for St. Louis encephalitis virus.

1968: First isolation of Vesicular Stomatitis virus (Indiana) from man in Panama and detection of virus transmission by the use of sentinel monkeys.

V. Medical Entomology:

1929: First elucidation of the human botfly, *Dermatobia hominis*, in man.

1935: First establishment of a laboratory colony of *anopheles albimanus*, the main vector of malaria in Central America.

1944: First tests of DDT to control phlebotomine sandflies.

1945: First experimental trials of DDT for the control of *Simulium* spp., the vectors of *Onchocerca volvulus*, the blinding filariid parasite of man.

1945: First experiments with DDT for the control of *Culicoides* sandflies.

1945: First observations in Panama on the habits and life histories of chigger mites *(Trombiculidae)*, potential vectors of disease.

1966: First comprehensive survey of the ticks and biting insects of Panama.

VI. Miscellaneous Projects:

1930-54: Comprehensive survey of the poisonous snakes of Panama and the incidence of snake bites.

SOURCE: Willard H. Wright, *40 Years of Tropical Medicine Research* (Washington, D.C.: Reese Press, 1970).

plan and carry out research related to tropical diseases without multiyear budgeting and some assurance of multiyear funding.

Gorgas itself could improve its standing and its relevance by:

- being more aggressive in its publishing,
- by making better use of its Advisory Scientific Board (see ch. 5 for examples of possibilities),
- by more actively seeking out associations and collaborations with a range of universities,

groups from other countries, and international organizations,
- by making strategic plans to move more fully into the developing areas of modern science (e.g., work with monoclonal antibodies and other immunological diagnostics, and biotechnology approaches to vaccine-related research and development), and
- by making more of an effort to run vigorous visiting scientist and fellowship programs.

OTA concludes that the only benefit to the United States of defunding Gorgas would be savings of perhaps significantly less than $2 million a year. The negative consequences would include loss of one of the few, high-quality, broadly relevant, tropical research institutions located in a tropical country. The standing of the United States in tropical America would inevitably suffer.

Ironically, GML is in danger of extinction at the very time that U.S. interest in Latin America is high, and at a time when tropical medicine has never been more relevant to U.S. interests.

In summary, OTA concludes that the positive consequences of U.S. core support of Gorgas greatly outweigh the amount of funds involved. Defunding now, followed by an appreciation of the loss later and a subsequent attempt to reinstate such a research capability, may result in much larger required investments, an inability to recreate successful conditions for quality research, or both.*

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*In fact, it may be impossible to recreate GML or a similar institution in the current political climate in Latin America (51).

BACKGROUND

The Tropics and Tropical Diseases

The Tropics can be roughly considered to include Central America, much of South America, the South Pacific, southern Asia, and most of sub-Saharan Africa. Tropical nations are usually characterized by poverty, substandard drinking water and sanitation, hot and humid climates, poor health services, low levels of education, and in some cases swampy or jungle areas. Annual per capita income is often extremely low (as low as or even less than $100). In tropical America, the average per capita gross domestic product was $1,500 in 1980. However, the variation is wide, ranging from nearly $9,000 in the Bahamas and $2,685 in Barbados (both figures may be deceptive) to $267 in Haiti and $568 in Bolivia (75).

Of the world's approximately 4½ billion people, about three-quarters live in less developed countries, most of which are tropical. Of the approximately 600 million population (1980 figures) of the Western Hemisphere, about 60 percent live in Latin America, most of which is tropical.

Health status is generally poor, with high rates of infant mortality (primarily due to malnutrition, lack of prenatal care, and diarrheal and respiratory infections), widespread infection with debilitating disease, and high mortality and morbidity rates from all diseases except certain chronic ones associated with a higher standard of living (such as some cancers).

Any definition of "tropical disease" is arbitrary. In its strictest sense, perhaps, a tropical disease is one found—for reasons of physical environment and climate or the presence of specific disease vectors—entirely or predominantly in tropical regions.

However, a more realistic, and more useful, definition includes those diseases or conditions—such as acute respiratory infection, tuberculosis, malnutrition, or cholera—that occur or could occur in many regions, but which are considerably more prevalent in tropical areas because of the social and economic conditions that characterize many tropical countries. In countries with very low per capita gross domestic products, inadequate or unsafe water supplies and sanitation, low levels of health care services, high levels of illiteracy, and similar conditions, certain diseases are able to flourish beyond the extent that would be predicted simply on the basis of climate.

The OTA assessment, including this technical memorandum, will consider "classic" tropical diseases such as malaria that fit the narrower definition, but it will more generally be guided by the broader definition. Thus, a more appropriate phrase to describe the subject of the assessment and the context in which Gorgas will be evaluated is "medicine and health in the tropics."

The direct economic and social impacts of widespread disease are obvious, but the most substantial economic impacts may be indirect ones, affecting a country's human resources and productivity. For example, a country whose population has an extremely high prevalence of debilitating disease loses labor resources, and productivity inevitably suffers.

In addition to the humanistic concern with the health and quality of life of people in tropical countries, and in addition to the stake that all developed countries have in the economic health and development of developing countries, there is a smaller, yet definite benefit that can accrue to the United States through support of tropical disease research and technology development. Tropical countries are no longer—if they ever really were—"exotic" far off lands seen only by adventurers. A great many people now travel to and live in tropical countries, as tourists, in the diplomatic or military service, or as employees of U.S. or multinational companies. The number of such people is most likely increasing.* "The tropics are coming closer and bringing their diseases with them" (69).

In addition, advances in tropical disease research can represent valuable knowledge in general medical science, particularly in the areas of infectious disease control, general preventive medicine, and environmental health.

The Value of Laboratories Located in the Tropics

Laboratories and field stations located in the Tropics have played a vital role in tropical disease research during this century. There is a certain point at which research taking place in temperate countries, even though aimed at eventually eliminating or controlling tropical diseases, can go no further, regardless of the quality of researchers or institutions. Initially, information about the occurrence (incidence, prevalence, case-fatality rates), natural history, and transmission of diseases is necessary for the rational design of strategies to deal with diseases, and this can only be collected in the field. Finally, the fruits of research—e.g., drugs and vaccines, vector control programs—must be tested where the diseases occur: in tropical regions. These are the very minimum involvements for institutions in the Tropics.

There is absolutely no substitute for field conditions in tropical countries. This point has been made to OTA time and again by tropical health experts in academia, Government research organizations, and the U.S. military.

Apart from research, training in tropical medicine can only reasonably take place in the Tropics. Training needs and expertise have traditionally been concentrated largely in the military. Additionally, professionals with training in tropical medicine are in demand by foreign governments, academic institutions, and voluntary agencies (107).

In addition to benefits to the U.S. population from knowledge of the control of tropical diseases, the existing tropical field laboratories benefit the countries in which they are located. The country's health science professionals who are involved in the projects or receiving training raise the level of sophistication of biomedical research in these countries. The disease problems studied are of obvious importance to the populations in these countries, and any progress in treatment or control will benefit them. An additional benefit can be a lessening of the "brain drain" that occurs in many, especially developing, countries. When a good quality research institution exists in a country, its professionals have a place and the opportunity to work and develop without emigrating and thus not depriving the country of their skills.

The U.S. Government supports a relatively small number of laboratories in tropical areas (see app. B). The Department of Defense operates eight medical research laboratories in the Tropics.

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*The increasing number of refugees in recent years serves as a dramatic example of an additional reason for regarding attention to tropical medicine as an important priority for the United States.

In Latin America, the Centers for Disease Control (CDC) operates the Medical Entomology Research and Training Unit in Guatemala. CDC previously ran a field station in El Salvador, which has been closed. The United States also supports tropical health research through contributions to international development agencies and through bilateral aid.

Establishing new field laboratories is a difficult and time-consuming task. Building good relations with the host country and becoming a productive unit may take years. The decision to eliminate an existing laboratory should consider that point.

Thus, any evaluation of GML must not only consider the quality and relevance of its research, but also its role as a research, training, and public health unit actually located in the Tropics.

Chapter 2

Gorgas Memorial Institute and Laboratory

Photo credits: Gorgas Memorial Laboratory

Front entrance to the Gorgas Memorial Laboratory, in Panama City, Republic of Panama (bottom photo). Photo at top shows the Laboratory complex in Panama City. At the extreme left is the side of the administrative offices; the lower connecting structure houses the Library; to the right rear are the research laboratories. The complex also contains animal buildings and an insect facility (insectory)

Chapter 2

Gorgas Memorial Institute and Laboratory

The Gorgas Memorial Institute of Tropical and Preventive Medicine, Incorporated (GMI), a private, nonprofit organization, was incorporated in Delaware and registered in the Republic of Panama in 1921 as a memorial to Major General William Crawford Gorgas (47).

The Gorgas Memorial Laboratory (GML), GMI's research arm and primary function, was established in 1928 in the Republic of Panama, with resources made available by the Governments of the United States and Panama and by several national and international agencies. The establishment of GML was made possible by an act of Congress (Public Law 70-350), which authorized a permanent annual contribution for the facility, provided that a site and building were made available from other sources, and by action of the National Assembly of the Republic of Panama, which granted land and a building on the condition that the property be used for a research laboratory (47).

The contribution made annually by the U.S. Government to GMI, which constitutes the core support for the maintenance and operation of GML, is administered by the Fogarty International Center (FIC) of the National Institutes of Health (NIH). Public Law 70-350, as amended, authorizes Congress to provide up to $2 million for GMI. In fiscal year 1983 GMI received $1.8 million through FIC, an increase from the fiscal year 1982 allotment of $1.692 million. Although GMI asked for $1.9 million in core support for GML in fiscal year 1984, the latest fiscal year 1984 NIH budget request targets no funds for GMI (47,115).

GML also receives grants and contracts supporting specific research projects from a variety of United States, Panamanian, and international organizations. In fiscal year 1982, total U.S. contributions including research grants from the U.S. Army, Navy, NIH, and the Agency for International Development totaled approximately $2,225,200, or 96.9 percent of all direct financial support for GMI/GML (see tables 3A and 3B).

Panamanian support for GML, which largely comes in the indirect form of property grants and a tax-favored status, is more difficult to tabulate. In 1930, the appraised value of the land donated by the Republic of Panama was $126,750. Estimates of the current value of the land and facilities have gone as high as $20 million by one senior Panamanian official, but no exact figure is available. In 1979, FIC estimated the value of the "in-

Table 3A.—Sources of Financial Support for the Gorgas Institute and Laboratory Fiscal Years 1975-82 (dollars in thousands)

	1975	1976	1977	1978	1979	1980	1981	1982	1975-82 total
U.S Appropriation	$ 707.5	$1,360	$1,400.0	$1,400.0	$1,700.0	$1,700.0	$1,800.0	$1,692.0	$11,759.0
National Institutes of Health	929.1	174.8	228.1	248.4	333.3	255.9	305.1	219.2	2,693.1
Health and Human Service (HEW)	—	—	—	—	4.4	4.7	0.9	—	10.0
U.S. Army	223.4	203.5	111.7	130.2	145.2	187.5	257.8	228.6	1,488.0
U.S. Navy	35.0	33.8	25.0	25.0	30.0	35.0	35.0	35.0	235.8
AID	120.0	5.5	—	—	8.1	23.3	45.2	—	202.1
Subtotal Federal support	$2,015.0	$1,777.6	$1,764.8	$1,803.6	$2,221.0	$2,205.5	$2,444.0	$2,174.9	$16,406.3
Other U.S. support	$ 7.3	$ 4.3	$ 2.7	—	$ 58.3	$ 89.5	$ 58.6	$ 50.3	$ 271.1
Total U.S. support	$2,022.3	$1,781.9	$1,767.6	$1,803.6	$2.279.2	$2,295.0	$2,502.6	$2,225.2	$16,677.5
Government of Panama	—	$ 59.3	$ 17.2	$ 37.1	$ 1.0	$ 308.4	$251.0	$22.5	$696.5
WHO/PAHO	$ 7.7	4.4	16.0	36.9	118.2	57.0	47.8	49.0	336.9
World Bank	—	—	—	6.9	—	—	—	—	6.8
Wellcome Laboratories	—	—	—	(a)	1.0	—	—	—	1.0
Total non-U.S. Support	$ 7.7	$ 63.7	$ 33.2	$ 80.8	$ 120.2	$ 365.4	$ 298.8	$ 71.5	$ 1,041.3
Total support	$2,030.0	$1,845.6	$1,800.8	$1,884.5	$2,399.5	$2,660.4	$2,801.4	$2,296.7	$17,718.7

[a] Less than $50.

Table 3B.—Sources of Financial Support for the Gorgas Institute and Laboratory Fiscal Years 1975-82
(as of percent)

	1975	1976	1977	1978	1979	1980	1981	1982	1975-82 average
U.S Appropriation	34.9	73.7	77.7	74.3	70.8	63.9	64.3	73.7	66.4
National Institutes of Health	45.8	9.5	12.7	13.2	13.9	9.6	10.9	10.0	16.7
Health and Human Service (HEW)	—	—	—	—	0.2	0.2	(a)	—	0.1
U.S. Army	11.0	11.0	6.2	6.9	6.1	7.0	9.2	10.0	8.4
U.S. Navy	1.7	1.8	1.4	1.3	1.3	1.3	1.2	2.0	1.4
AID	5.9	0.3	—	—	0.3	0.9	1.6	—	1.1
Subtotal Federal support	99.3	96.3	98.0	95.7	92.6	82.9	87.2	94.7	92.6
Other U.S. support	0.4	0.2	0.2	—	2.4	3.4	2.1	2.2	1.5
Total U.S. support	99.6	96.5	98.2	95.7	95.0	86.3	89.3	96.9	94.1
Government of Panama	—	3.2	1.0	2.0	(a)	11.6	9.0	1.0	3.9
WHO/PAHO	0.4	0.2	0.9	2.0	4.9	2.1	1.7	2.1	1.9
World Bank	—	—	—	0.4	—	—	—	—	(a)
Wellcome Laboratories	—	—	—	(a)	(a)	—	—	—	(a)
Total non-U.S. Support	0.4	3.5	1.8	4.3	5.0	13.7	10.7	3.1	5.9
Total support	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

[a] Less than 0.05 support.

SOURCE: Gorgas Memorial Institute, 1983.

direct services" provided each year by the Panamanian Government to be $175,000.

GMI is required by law to make an annual report to Congress on the activities and expenditures of the laboratory. The U.S. General Accounting Office (GAO) audited all GMI/GML financial statements until 1980 (47).

GML is currently engaged in an effort to cut costs and broaden its financial base of support. This issue is being addressed in the related GAO study, and will not be covered in this technical memorandum. Plans call for the the closure of Building 265, which cost an estimated $279,102 to maintain in fiscal year 1982 (see table 4); however, modifications to accommodate the relocation of the virology program formerly housed in the building are estimated at a one-time cost of $250,000 (table 5 shows this figure, as well as other projected costs for fiscal year 1984).

The Laboratory has just finished terminating the employment of some 29 of GML's employees and staff. The closing of the entire bacteriology department eliminated three Panamanian scientists with 10 to 22 years tenure at GML (121). GMI sought relief from the Panamanian Minister of Health and Minister of Labor from penalty charges attributable to early termination of Panamanian employees (47), but waivers were not granted. GMI has established a Development Committee to explore fund-raising possibilities in the private sector. Because of the completion of a number of commissioned projects, revenues from research grants and contracts dropped from $995,641 in fiscal year 1981 to $594,224 in fiscal year 1982. As a result of this decline, the proportion of total funding represented by U.S. core support rose from 64.3 percent of all revenues in fiscal year 1981 to 73.7 percent in fiscal year 1982.

Of the $1,884,824 spent by GMI/GML over the 12-month period ending July 1983 after the reduction-in-force, over half ($928.101) went towards salary costs. Utility charges, including those for Building 265, came to $413,257. Administrative costs accounted for $130,732, and another $163,258 was spent to maintain the GMI office in Washington, D.C. The "direct" nonsalary research dollars amount for the laboratory was $209,476 (121).

At its headquarters in Washington. D.C., GMI is governed by a 47-member Board of Directors, which includes officials of the Governments of the United States and Panama, representatives of national and international agencies active in areas of common interest, and U.S. and Latin American scientists and professionals. The board meets annually to determine the policies of the organiza-

Table 4.—Gorgas Memorial Institute of Tropical and Preventive Medicine, Incorporated: Operating Budgets Fiscal Years 1982 and 1983

	Fiscal year 1982		Fiscal year 1983 Program Budget	
	Budgeted (1/20/82)	Actual unaudited	Old	New
Revenue:				
Contribution by the United States	$1,692,000	$1,692,000	$1,800,000	$1,800,000
Research grants and contracts	609,407	594,224	346,209	346,209
Other	2,500	10,442	10,000	10,000
Subtotal	2,303,907	2,296,666	2,156,209	2,156,209
Additional revenue required	386,888	—	390,930	524,011
Total revenue required	2,690,795	2,296,666	2,547,139	2,680,220
Expenditures:				
Core—				
Infectious Disease Program				
Virology	275,390	340,752	383,547	374,146
Bacteriology	105,765	110,826	114,741	183,052
Parasitology	78,515	85,053	79,565	73,920
Immunology	21,430	21,585	35,364	48,166
Clinical	71,297	81,809	60,366	67,688
Total	552,397	640,025	673,583	746,972
Ecology & Epidemiology Program				
Ecology	110,216	95,840	105,155	106,586
Vertebrate Zoology	42,474	39,831	41,039	41,039
Entomology	17,000	15,801	18,029	18,029
Epidemiology	494	6,664	9,331	9,331
Vector Biology	143,839	158,478	139,477	139,477
Total	314,023	316,614	313,031	314,462
Primatology & Laboratory Animals Program				
Animal Models	46,254	47,350	57,754	53,954
Animal Colony	73,546	81,969	85,977	88,427
Total	119,800	129,319	143,731	142,381
Education & Technical Support Program				
Educational Programs	5,425	4,346	6,139	5,639
Library	57,991	56,829	62,451	71,056
Total	63,416	61,175	68,590	76,695
Data Processing	43,712	36,777	39,551	45,738
Administration				
Washington, D.C.	161,256	146,242	163,258	163,258
Panamá	326,647	256,095	313,609	330,765
Total	487,903	402,337	476,867	494,023
Maintenance				
Panamá	232,992	269,449	277,804	290,539
Building 265	309,693	279,102	290,583	321,011
Total	542,685	548,551	568,387	611,550
Seniority Premium	25,000	21,028	15,000	
Total core expenditures	2,148,936	2,155,826	2,298,740	2,431,821
Direct grant and contract expenditures	541,859	445,089	248,399	248,399
Total expenditures	2,690,795	2,600,915	2,547,139	2,680,220
Excess revenue over/(under) expenditures	$ -0-	$ (304,249)	$ -0-	$ -0-

SOURCE: Gorgas Memorial Institute, 1983.

tion, review the managerial and fiscal operation, approve budgets, and elect officers, Board members, and advisors. Between meetings, the Board's functions are delegated to the 9-member Executive Committee, which meets monthly under the chairmanship of the President of GMI, Dr. Leon Jacobs, a Scientist Emeritus of NIH. The 24-member Advisory Scientific Board, consisting of scientists in various disciplines, is to advise on the development and review of scientific programs

Table 5.—Gorgas Memorial Institute of Tropical and Preventive Medicine, Incorporated: Projection Fiscal Year 1984

Revenue:	
Contribution by the United States	$1,899,000
Research grants and contracts	300,000
Other	10,000
Subtotal	2,209,000
Additional revenue required	18,000
Total revenue required	2,227,000
Expenditures:	
Core—	
Epidemiology	180,509
Microbiology	276,237
Tropical Ecology	326,553
Applied Pharmacology	165,699
Administrative Services & Training—Panamá	913,553[a]
Administration—Washington, D.C.	177,000
Total core expenditures	2,039,551
Direct grant and contract expenditures	187,449
Total expenditures	2,227,000
Excess revenue over/(under) expenditures	$ -0-

[a] Includes $250,000 for anticipated facilities renovation.

SOURCE: Gorgas Memorial Institute, 1983.

and, if plans are fulfilled, to serve as an editorial review board for GML staff's scientific manuscripts.* The officers, members, and advisors serve without compensation (47).

In 1972, the Middle American Research Unit, which had been in existence since about 1960 in the Canal Zone as an offsite laboratory of the National Institute of Allergy and Infectious Diseases (NIAID), was merged with GML. At the end of fiscal year 1975, NIAID concluded its support for the work formerly done by this unit with a resulting loss of senior personnel and financial support for GML (110).**

ORGANIZATION

The organization of research activities of GML is currently undergoing change. Previously (and still officially) GML was divided among four scientific programs (see fig. 1). The Infectious Diseases Program was divided into Virology, Bacteriology, Parasitology, Immunology, and Clinical sections. The Ecology and Epidemiology Program was responsible for Vertebrate Zoology, Entomology, Epidemiology, and Vector Biology. Animal Models, Primate Biology, and Animal Colony research were under the Primatology and Laboratory Program. Education and Technical Support programs handled the Library, Photo-Laboratory, and Educational sections. In additon, GML maintained administrative and data processing sections.

Tentative plans for departmental reorganization have been drawn up, but will not be implemented until GML's financial situation is more secure (121). The new organization will include divisions for epidemiology, laboratory sciences (e.g., immunology, parasitology, serum bank), environmental biosciences (e.g., vector bionomics, ecology), clinical therapeutics (e.g., animal models, clinical investigation), and support services (library, administration, etc.). Figure 2 illustrates the proposed organization.

The interdisciplinary scientific staff of six Americans, nine Panamanians, and one Peruvian includes entomologists, arbovirologists, parasitologists, and other specialists (see table 6). One U.S. Navy medical officer and one Navy Ph. D. parasitologist are currently on GML's scientific staff. The director of GML, Raymond H. Watten, M.D., previously the commanding officer at the Navy's Medical Research Unit in Cairo, oversees a total of 94 staff members and employees (121).

GML is strategically located for studies of disease transmission and movement in tropical America. Panama is a crossroad of transportation in the region and GML itself is in close proximity to the field. GML also benefits from an available supply of *Aotus* monkeys, a simian valuable for the study of human malaria (110). The U.S. Fish and Wildlife Service classifies the *Aotus* as an animal which could become endangered by international trade.

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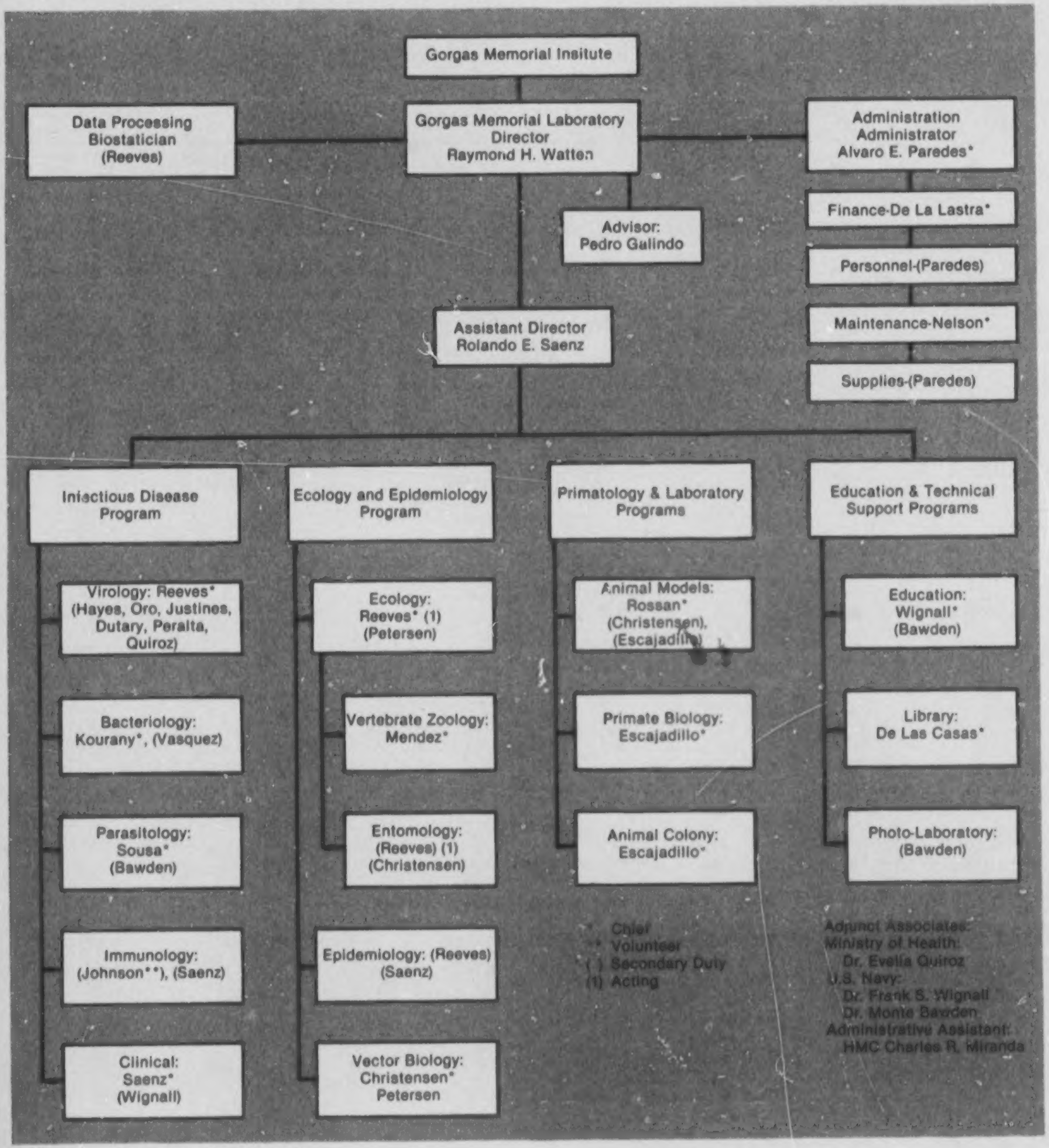
*See the GAO report for a review of the activities of the Advisory Scientific Board.

**Because of a deteriorating political situation, the Centers for Disease Control was forced to close its own Central American Research Center located in El Salvador in 1981 and relocate to a smaller research and training unit in Guatemala (53).

Figure 1.—Gorgas Memorial Institute Organization (currently official, but in process of being changed)

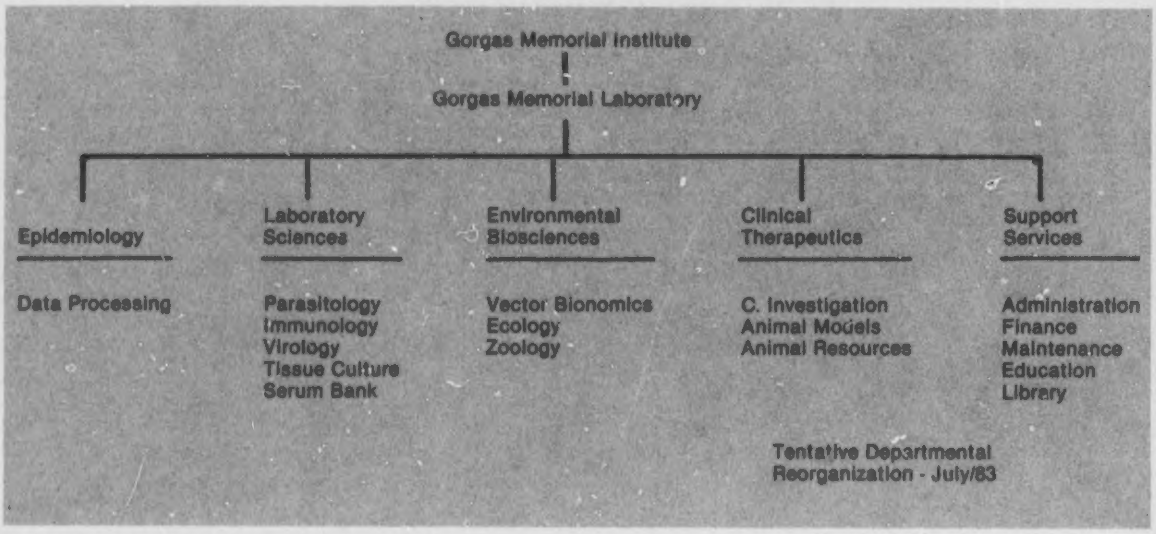

Gorgas Memorial Insitute
Data Processing
Biostatician
(Reeves)
Gorgas Memorial Laboratory
Director
Raymond H. Watten
Administration
Administrator
Alvaro E. Paredes*
Finance-De La Lastra*
Personnel-(Paredes)
Maintenance-Nelson*
Supplies-(Paredes)
Advisor:
Pedro Galindo
Assistant Director
Rolando E. Saenz
Infectious Disease
Program
Virology: Reeves*
(Hayes, Oro, Justines,
Dutary, Peralta,
Quiroz)
Bacteriology:
Kourany*, (Vasquez)
Parasitology:
Sousa*
(Bawden)
Immunology:
(Johnson**), (Saenz)
Clinical:
Saenz*
(Wignall)
Ecology and Epidemiology
Program
Ecology:
Reeves* (1)
(Petersen)
Vertebrate Zoology:
Mendez*
Entomology:
(Reeves) (1)
(Christensen)
Epidemiology: (Reeves)
(Saenz)
Vector Biology:
Christensen*
Petersen
Primatology & Laboratory
Programs
Animal Models:
Rossan*
(Christensen),
(Escajadillo)
Primate Biology:
Escajadillo*
Animal Colony:
Escajadillo*
Education & Technical
Support Programs
Education:
Wignall*
(Bawden)
Library:
De Las Casas*
Photo-Laboratory:
(Bawden)

* Chief
** Volunteer
( ) Secondary Duty
(1) Acting

Adjunct Associates:
Ministry of Health:
Dr. Evelia Quiroz
U.S. Navy:
Dr. Frank S. Wignall
Dr. Monte Bawden
Administrative Assistant:
HMC Charles R. Miranda

SOURCE: Gorgas Memorial Institute, July 1982.

Figure 2.—Gorgas Memorial Institute-Proposed Organization Chart


Gorgas Memorial Institute
Gorgas Memorial Laboratory
Epidemiology
Data Processing
Laboratory Sciences
Parasitology
Immunology
Virology
Tissue Culture
Serum Bank
Environmental Biosciences
Vector Bionomics
Ecology
Zoology
Clinical Therapeutics
C. Investigation
Animal Models
Animal Resources
Support Services
Administration
Finance
Maintenance
Education
Library
Tentative Departmental Reorganization - July/83

SOURCE: Gorgas Memorial Laboratory, 1983.

Table 6.—Gorgas Memorial Laboratory Information on Scientific Staff as of July 1983

Watten, Raymond H., M.D. (U.S.)
  Director
Saenz, Rolando E., M.D. (Panamanian)
  Assistant Director
Adames, Abdiel J., Ph. D. (Panamanian)
  Ecologist Entomologist
Christensen, Howard A., Ph. D. (U.S.)
  Entomologist
Dutary, Bedsy C., Ph. D. (Panamanian)
  Arbovirologist
Escajadillo, Alfonso, D.V.M. (Peruvian)
  Medical Veterinarian
Justines, Gustavo, Ph. D. (Panamanian)
  Virologist
Kourany, Miguel, M.P.H., Ph. D. (Panamanian)
  Bacteriologist
Mendez, Eustorgio, Ph. D. (Panamanian)
  Vertebrate Ecologist
Oro, Gladys, M.S. (Panamanian)
  Microbiologist
Peralta, Pauline, Ph. D. (U.S.)
  Virologist
Petersen, John L., Ph. D. (U.S.)
  Insect Geneticist
Reeves, William C., M.D. (U.S.)
  Medical Virologist
Rossan, Richard N., Ph. D. (U.S.)
  Parasitologist-Primatologist
Sousa, Octavio E., Ph. D. (Panamanian)
  Parasitologist
Vasquez, Manuel A., M.D. (Panamanian)
  Physician-Microbiologist

SOURCE: Office of the Director, Gorgas Memorial Laboratory, July 1983.

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ACTIVITIES OF GML

The activities at GML can be characterized as basic and applied biomedical research, public health and medical services, and training. Projects use the laboratory, the clinic, and the field as bases. Neither the types of activities nor the areas where they are carried out are entirely categorical or mutually exclusive. The border between basic and applied research, for instance, is not a clean line. Basic biomedical research, as used in this paper, refers to work that seeks to advance the state of knowledge about the vital processes that underlie the normal functioning of organisms and their malfunctioning in disease. Applied biomedical research draws upon basic information to develop means of prevention, treatment, and cure of disease (4).

At the two ends of the research spectrum, the distinction is clear. Observing and characterizing the physical and metabolic behavior of a malarial parasite is basic research. Using the information gained in that way to design an intervention, e.g., a vaccine or drug therapy, is applied research. Further down the line, e.g., testing the drug or vaccine in nonhuman primates, a major line of research at Gorgas, the work falls farther toward the applied end of the spectrum. A clinical trial of the intervention in humans is a final step before research turns to practice. Even during a clinical trial, however, observations can be made that would fit the definition of basic research, in furthering the basic knowledge of normal and abnormal human functioning. Marking the checkpoint between basic and applied research in the process described is all but impossible, and to spend a great deal of time attempting to do so is unproductive.

Many projects at GML have both research and service components. About 1,000 patients per year are treated in the clinic, providing an important service to the community. Observations of those patients are an important source for learning about the natural history and treatment of diseases, many of which cannot be adequately studied elsewhere.

GML began as a traditional tropical medicine research institute concentrating on studies of malaria, trypanosomiasis, and leishmaniasis. In recent years, attention has been increasingly directed to arboviruses and their vectors (110). Currently, GML also is involved in research projects concerning sexually transmitted diseases, specific cancers, and ecological studies (see table 7 for a more detailed listing of areas of activity). In the past, GML has been called on to serve as a reference center for the region (76). GMI also offers "Medicine in the Tropics," a 6-week tropical medicine training program offered primarily to physicians from the U.S. Navy, intended to prepare the medical officers for operational assignments in tropical areas. GML also hosts predoctoral and postdoctoral students and scientists. In 1981, students came from Venezuela, Costa Rica, Panama, and the United States; in 1982, from Kenya, Hungary, Argentina, Brazil, Cuba, Panama, and the United States. In the past 12 months, GML lists these training figures (121):

30	Students, *Medicine in the Tropics* (6-week course)
25	Visiting scientists
1	Postdoctoral student
2	Predoctoral students
3	Bachelor-level students
6	Trainees and graduate students

GML has working relationships with the Medical Entomology Research and Training Unit in Guatemala, the Centers for Disease Control, NIH, Louisiana State University (LSU), Johns Hopkins University, and other academic and scientific institutions. Most of these arrangements are "informal," but GML has a Memorandum of Agreement with LSU, Yale University, Johns Hopkins, and the University of Panama (121).

Table 7.—Recent Activities of Gorgas Memorial Laboratory

Area of activity	Active/recent	Funding
Animal colonies	A	Core
Care and maintenance of experimental animals		
Applied pharmacology:		
Malaria drug testing (*Aotus* studies) (also under Malaria)	A	U.S. Army contract
Rabies, clinical trial to identify best minimal dose of human diploid vaccine	R	Core, with MOH
Arboviruses (various):		
Arbovirus survey in Tabasara River Basin	R	Contract
Various projects relating to characterization of arboviruses and investigating outbreaks		
Aseptic meningitis	R	Core
Blackflies:		
Vector competence of *S. quadrivittatum* for *O. volvulus*	R	Core, with Johns Hopkins University
Blackfly control in Fortuna Hydroelectric project Species bionics; intervention at breeding sites		
Blood meal analysis:		
Feeding habits of known and potential vectors	A	Core and WHO TDR
Campylobacter:		
Survey of this important cause of diarrhea in Panama	R	Core
Cancer:		
Human T-cell leukemia virus	A	Core and NCI grant
Cervical and penile cancer in Herrera Province	A	Core
Association with HTLV; and with herpes simplex		
Cervical cancer and Herpes simplex	A	Core, with McMaster University
Cell culture lines:		
Culturing of Sloth kidney cells	A	Core
Culturing of *haemogogus equinus* cells		
Chagas' disease:		
Study of risk of infection and human manifestations of Chagas' disease transmitted by *R. pallescens* (Central Panama) and *T. dimidiata* (Western Panama)	A	WHO TDR grant (partial)
Biological and Isozyme characterization of *T. cruzi* and *T. rangeli* strains	A	Core
Clinical diagnosis and treatment (approximately 1,000 cases per year)	A	Core, with MOH
Data Processing:		
National Cancer Registry (Panama)	A	Core, plus miscellaneous
Cervical cancer project		
National serologic survey		
Bayano Lake clinical surveillance project		
Malaria chemotherapy project		
STD Project		
Environmental Impact Assessement:		
Tabasara Hydroelectric Project	R	Contract
Fortuna River	R	Contract
Influenza and clinical diagnostic virology services and surveillance	A	Core, with MOH
Leishmaniasis:		
Identification of vector special; identification of reservoir (porcupine)	A	Core and WHO TDR grant
Isozyme electrophoresis diagnosis of strain and species of *Leishmania* and identification of leishmaniasis vectors	A	Core and WHO TDR grant
Library:		
Reference service and collection available to staff and outside researchers	A	Core and grant from Panama
Malaria:		
In Vitro cultivation of infectious agent	R	AID grant
Antimalarial Drug Testing in *Aotus* monkey	A	U.S. Army contract
Phlebotomus fever:		
Serologic surveys of U.S. troops and Panamanians for Chagres and Punta Toro Fevers	R	Core
Comparison of Punto Toro and Rift Valley Fevers	R	Core
Identification of amplifying host vertebrates	R	Core
Retinochoroiditis due to Toxoplasmosis	R	Core
Serum Bank Reference Collection	A	Core

Table 7.—Recent Activities of Gorgas Memorial Laboratory—Continued

Area of activity	Active/recent	Funding
Sexually transmitted diseases (STDs):		
Gonorrhea—survey of prostitutes on prevalence and penicillin resistance	R	Core
Epidemiology of STDs in Panama (prevalence; maternal STD and effect on pregnancy outcomes)	A	Core, with MOH
Shigellosis:		
Study of drug resistance in shigella isolates	R	Core
St. Louis encephalitis (SLE):		
Study of how virus is maintained in the tropics	R	NIH grant
Studies with olivaceous cormorant	R	NIH grant
Susceptibility to infection of Panamanian vector with three geographic isolates of SLE virus	R	NIH grant
Virulence testing and RNA fingerprinting of Panamanian SLE virus isolates	R	NIH grant
Training:		
Medicine and health in the Tropics	A	U.S. Navy
Triatoma Colony maintained for xenodiagnosis	A	Core
Trypanosomiasis	A	Core and WHO grant
Venezuelan equine encephalitis (VEE):		
Search for epizootic virions from enzootic strains	A	Core
Vertebrate zoology		
Survey of Mammalian Fauna of Panama	R	Core
Long-term survey of rodents (zoogeography)	A	Core
Studies of Ectoparasites	A	Core
Yellow fever:		
Monitoring of animal reservoirs	A	Core
Monitoring of epizootics in Spider monkeys		
Monitoring of variations in vectors' ability to transmit virus	A	Core
Genetic studies of jungle vectors	R	NIH grant
Longevity and age structure of Sylvan Yellow fever vectors	R	NIH grant

KEY: AID—U.S. Agency for International Development; MOH—Panamanian Ministry of Health; NCI—National Cancer Institute; NIH—National Institutes of Health; TDR—Special Programme for Research and Training in Tropical Diseases (WHO); WHO—World Health Organization.

SOURCE: Office of Technology Assessment, 1983. information provided by Gorgas Memorial Laboratory; WHO; and Gorgas Memorial Laboratory fiscal year 1981 and 1982 reports.

Chapter 3

Quality of Research at the Gorgas Memorial Laboratory

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Quality of Research at the Gorgas Memorial Laboratory

INTRODUCTION

The Gorgas Memorial Laboratory (GML) engages in a wide range of public health, research, and training activities. Gorgas scientists work in the laboratory, in the field, and in the medical clinic. GML performs applied and basic research, and provides public health services in those settings. (See ch. 2 for a description of current activities.)

This chapter examines the quality of research, training, and public health activities at GML. Ideally, assessing the quality of the work at GML would be accomplished by a review of each project in each program. A multidisciplinary team of scientists would visit GML, speak with investigators, review research protocols, procedures, and publications, and evaluate the physical plant. An overall rating would then be made, pointing out strong and weak points. Such a thorough review would serve as the basis for recommending changes in current programs, and to point out areas with future potential. OTA was unable to take such an approach.

Another avenue for assessing the quality of GML activities, and one that was suggested to the Office of Technology Assessment (OTA) by a number of people, is to compare GML activities and its record of productivity with that of a similar institution. The logical choices for such a comparison might be, e.g., Institute of Nutrition of the Caribbean and Panama, International Laboratory of Research on Animal Diseases, the Department of Defense (DOD) medical research units, or the Centers for Disease Control's former field station in El Salvador. Even these institutions, however, are very different from GML in their administrative structures and their research agendas. While it was possible with the time available and information at hand to make gross comparisons of GML and DOD budgets, it was not possible to make adequate comparisons of the quality of scientific activities.

For its review, OTA relied on:

1. the record of past scientific review of GML's programs;
2. a review of recent publications by GML researchers, including an in-depth analysis of a selection of active manuscripts and published articles;
3. an assessment of peer review at GML;
4. a review of recent grants and contracts held by GML; and
5. the results of a telephone survey, commissioned by OTA, of experts familiar with GML.

OTA is aware that this type of assessment is not definitive. It relies heavily on circumstantial evidence about quality (e.g., number of publications), some unsubstantiated opinions about quality (e.g., comments from the telephone survey), and the opinions of site visitors in previous years. As discussed above, other, more detailed methods of assessment are possible which would both give a better reading of the state of GML activities and serve as a guide for future directions. Such an assessment could be valuable to GML as well as its funding agencies, and might be considered as a GML priority for the near future.

SITE VISITS BY THE FOGARTY INTERNATIONAL CENTER

The Fogarty International Center (FIC) at the National Institutes of Health (NIH) has conducted two site visits to GML, one in 1976 (110) and the other in 1980 (111). In 1978, a review of all programs was carried out by a team with representatives from FIC and the Gorgas Memorial Institute

(GMI) Executive Committee and Advisory Scientific Board. These are the only comprehensive program reviews that have taken place in recent years. A scheduled site visit for 1983 has been postponed due to the uncertainties surrounding GML's future (57). Before those site visits, committees of GMI's Advisory Scientific Board had conducted reviews of the virology and parasitology programs in 1973 and 1974, respectively.

The FIC site visits were conducted by multidisciplinary teams which evaulated the scientific activities at GML. The charge of the 1980 five-person team was:

> . . . an examination of the scientific programs of the Laboratory as to their quality, adequacy, and relevance in furtherance of the mission of the laboratory, to provide advice and to make recommendations as to any alterations in priorities and program or project implementation that seemed indicated, and in the final analysis to arrive at some composite judgment as to the value of the scientific work relative to the investment by the U.S. Government.

In addition to reviewing the research programs, the site visit report comments on administrative operations and GML's program in tropical medicine training.

Both FIC site visit reports were strongly positive about the overall operation of GML, while identifying weaknesses and areas of unused potential. The 1980 report concludes:

> The core long-range program emphases of the GML on parasitology, arbovirology, and ecologic studies continue to be of scientific importance, relevant to the health concerns of the United States, Panama, and the region, and appropriate to the unique location and facilities offered by GML.
>
> The overall quality of research conducted by GML is of high standard, nationally (United States) and internationally. As with any institution undertaking a broad spectrum of projects, there are unevennesses that necessitate periodic review and reevaluation, especially in terms of priority relative to available resources. The Team felt that, in general, this [review and reevaluation] was being done conscientiously and well. It would emphasize, as the previous FIC review did, that GMI actively continue to support the GML Director in this respect through regular site visits by members of the Executive Committee and/or the Advisory Scientific Board.

The 1980 report noted a strengthening and consolidation of research activities since the previous (1976) site visit. A major factor facilitating that improvement was the relatively stable funding through the core grant, after several years of "uncertainty and adjustments" associated with GML's absorption of the former NIH Middle America Research Unit (MARU). At this time, adjustments are continuing, as described in chapter 2. Equilibrium has not yet been reached, and the research programs may be affected to some degree, particularly in terms of long-range planning, until the reorganization is complete.

Review of Research Programs

The FIC team critiqued each program as to its quality and relevance, and developed specific recommendations for each. The findings and recommendations of the 1980 site visit report are summarized below.

Parasitic Infections

Programs in leishmaniasis, trypanosomiasis, malaria, and toxoplasmosis are critiqued separately. In general, these diseases are considered to be important in Panama. The site visit report, however, pointed out the need for refocusing some of the studies.

The report stressed the unique availability of large numbers of patients with leishmaniasis, and the potential for expanding and redirecting efforts in clinical investigations. Ongoing research with a known major animal reservoir of leishmaniasis, the two-toed sloth, is promising, and could also be more carefully focused.

GML has conducted research on Chagas' disease (American trypanosomiasis) for many years. Although GML is in possession of a large pool of clinical data, little has been published. The site visitors suggested that a major contribution to understanding the importance of Chagas' disease in Panama could result from analysis and publication of clinical observations. GML had made some interesting observations about treatment of

Chagas' disease with metronidazole, which the site visit team thought worthy of followup by other laboratories. Studies of vectors and animal reservoirs, and longitudinal prevalence studies in one population had provided interesting information, but the goals of those projects required reevaluation.

Malaria

The main activities in malaria research are drug testing for the U.S. Army, in *Aotus* monkeys. This work is considered important, but the site visitors recommended expanding the scope of malaria research to make greater use of the expertise and resources at GML.

Toxoplasmosis

Toxoplasmosis is a major cause of chorioretinitis (inflammation of parts of the eye) in Panama, and as such is important, although, according to the site visit report "not of the highest priority." While the site visit team thought contributions could be made toward understanding toxoplasmosis, "the principal focus of the project as described seems somewhat lacking in relevancy."

Arbovirus Program

Yellow fever, Venezuelan equine encephalomyelitis, and St. Louis encephalitis are the major arboviral diseases studied at Gorgas, though GML retains the capability to investigate and evaluate outbreaks of other diseases.

Yellow Fever

The site visit report deemed the yellow fever surveillance "one of the most important programs of GML." Panama is the key location for early detection of spreading yellow fever from Colombia into Central America. Gorgas has developed a proven method for surveillance of wild howler and spider monkeys, the animal reservoirs of yellow fever. At this time there is no alternative method. The report favored continuation of monitoring seasonal variations in known mosquito vectors of yellow fever, and expanded efforts in studying transmission of yellow fever.

Venezuelan Equine Encephalomyelitis (VEE)

Past efforts in VEE research have produced useful information. The site visit report suggests expanding in this area.

St. Louis Encephalitis (SLE)

Comments on the SLE research program indicate that they are headed in productive directions and the work should be continued.

Environmental Assessment Program

Assessments of two major hydroelectric schemes have been carried out under contract to the Panamanian power authority. Although very different in nature from most of the activities taking place at GML, these assessments were considered successful and useful by the site visitors. They concluded:

> In addition to their technical and social importance, such environmental assessment projects can help provide a model for similar studies in other parts of the developing and developed world. Furthermore, they can readily be perceived by the public as dealing with actual concerns of that country's society. We feel that more than anything else in recent years, these projects in Panama have probably helped improve the image of the GML in the eyes of Panamanians.

Diarrheal Diseases Program

Several projects in diarrheal diseases were in progress at the time of the site visit. They were of variable quality and relevance, according to the report. For instance, a project demonstrating the efficacy of oral fluid therapy in the treatment of dehydration secondary to acute diarrhea duplicated research done elsewhere, but the project appeared to be beneficial nonetheless. The report states:

> Although the merits of the project as original research are relatively low, the project served as an educational effort of considerable importance.

A study of travelers' diarrhea in Panamanian visitors to Mexico was considered of only secondary importance and not central to the mission of GML.

At the time of the site visit, a collaborative arrangement with the Johns Hopkins University School of Medicine had produced worthwhile results in studying the incidence of acute diarrheal disease in the San Blas Islands with respect to the availability of water. However, the Hopkins unit was not refunded beyond 1980 and the research was terminated.

Sexually Transmitted Diseases

Studies in sexually transmitted diseases (STDs) were carried out in collaboration with the Panamanian Ministry of Health. They have focused on the epidemiology and etiology of STDs, and have led to further studies bearing on the very high rate of cervical cancer in Panama. The site visit report commented that STD research was of "secondary importance" to the other major programs in parasitology, arbovirology, and environmental impact studies.

Cancer Registry/Cancer of the Cervix

GML has worked with the Panamanian national cancer registry in epidemiologic studies of cervical cancer. Analysis of registry data indicated that Panama has one of the highest rates of cervical cancer in the world, and that geographic clusters in certain provinces have extremely high rates. Though not considered of the highest priority by the site visitors, they rated the work of high quality and recommended that it be continued.

Training

The site visit team was enthusiastic about the excellence of training provided in the "Medicine in the Tropics" course. To be more consistent with the mission of GML, however, it was suggested that Panamanians be included in the course on a regular basis* and that GML take over the direction of the course entirely, rather than the director being a U.S. Navy assignee. They concluded:

> . . . it appears that the training capabilities and opportunities offered by GML, including the Lister Hill fellowships of GMI itself, warrant wider notice in the scientific community.

Publications

Research and scientists are often judged on their publication records. The number of publications, the journals in which they are published, and the number of other authors who later cite the papers are some objective, though indirect, indicators of quality. However, there are no fixed standards against which to make a judgment of excellence. Research activities, in general, are aimed toward publishing results, while public health service activities do not have publication as a primary goal. Even in research, each field of study and type of research varies greatly, and may result in a different array of publications. Long-term field surveillance studies may result in a major publication only after several years. Clinical observations may be published as case reports after only a single visit.

Environmental assessments are performed under contract to development agencies or companies, and may result in few external publications, though they may be quite successful. Surveillance activities are routine until something is found. In Panama, yellow fever outbreaks have occurred every 8 or 9 years, but surveillance must go on continuously.

Given the above perspective, OTA examined the GML publication record by looking at the number of publications in recent years and the journals in which they were published, and by evaluating the quality of a sample of recent publications and active manuscripts.

Number of Publications and Journals of Publication

Over the years of its existence, GML researchers have been authors or coauthors of about 950 published scientific papers, about 200 of them since 1975. (App. C lists publications since 1975.) Though it is impossible to rate the number of publications on a meaningful, objective scale, GML's record is indicative of continuous publishing activity. Table 8 shows the number of publications by GML staff by year. Whether more publications should have been expected is a subjective matter. A comparison of GML scientists' publishing record to that of six of the

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*According to the Director of GML, only one or two Panamanians take the 6-week course each session (121).

Table 8.—Total Publications of the Gorgas Memorial Laboratory, 1975-83

Year	Total articles appearing
1975	34
1976	18
1977	14
1978	7
1979	16
1980	24
1981	10
1982	17
1983 (to date)	6

SOURCE: Office of Technology Assessment, 1983. Based on data provided by Gorgas Memorial Laboratory, Office of the Director, Raymond Watten, July 1983.

centers supported by the Rockefeller Foundation's Great Neglected Diseases program shows GML to be at an acceptable but rather low level. GML scientists should certainly give more attention to publishing the results of their work, and GMI/GML management should be aggressive in urging such activity (the Director of GML and the President of GMI have indicated they share this view).

GML researchers publish in a variety of scientific journals. Table 9 lists the journals in which papers have appeared since 1980. These are largely refereed journals, meaning that papers are scrutinized in some formal way before acceptance, and generally there is some competition for publication.

Table 9.—Gorgas Memorial Laboratory: Publication Location for Articles Written by Staff; 1980 to July 1983

Journal or other location:	Number of publications
American Journal of Tropical Medicine and Hygiene	15
Revista Medica de Panama	13
Revista Medica de la Caja de Seguro Social	3
Applied and Environmental Microbiology	2
Infection and Immunity	2
American Museum of Novitates	2
Journal of Medical Virology	2
Journal of Medical Entomology	1
Mosquito News	1
Epidemiological Bulletin	1
Ecological Entomology	1
Bulletin of the WHO	1
Revista de Biologica Tropical	1
Journal of Pacific Insects	1
Transactions of the Royal Society of Tropical Medicine and Hygiene	1
Entomological and Ecological Studies	1
International Journal for the Study of Animal Problems	1
Journal of Infectious Diseases	1
Journal of the National Cancer Institute	1
Journal of Wildlife Diseases	1
New England Journal of Medicine	1
Journal of Economic Entomology	1
Revista Medico Cientifica	1
Annals of Internal Medicine	1
Mosquito Systematics	1
PAHO Workshop	1
BOOKS	2
Bacterial Infections of Humans	
Paediatric Cardiology	
Presentations at Symposia/Conferences	3
Total articles appearing	64

SOURCE: Office of Technology Assessment, 1983. Data from Office of the Director, Gorgas Memorial Laboratory, Raymond Watten, July 1983.

In most cases, Gorgas investigators were the principal authors (listed first among the authors, and generally taken to mean that the ideas and most of the work can be attributed to that individual). Publications appear in both English and Spanish language journals. In general, papers of direct relevance to medical practice in tropical America appear in Spanish language publications (e.g., *Revista Medica de Panama*). Those of more global interest have appeared in journals with more international circulation (e.g., *The American Journal of Tropical Medicine and Hygiene*). An example of a subject of interest both locally and internationally is oral rehydration therapy of infantile diarrhea. On the basis of clinical research carried out at GML, a paper was published in 1980 in *Revista Medica de Panama* (6). The research and resulting publication was of great value to local physicians in demonstrating the value of oral rehydration. Subsequently, the same research served as a basis for the Panamanian arm of a controlled study of oral rehydration therapy of children in the United States and Panama, which was published in the *New England Journal of Medicine* (95). An editorial accompanying the article (12) highlighted the importance of this work, making the point that "Western-trained pediatricians . . . have created major impediments . . . to the promulgation of oral-rehydration treatment . . . Indeed, local herb doctors, quick to recognize the value of oral rehydration, have often been more helpful than their Western-trained colleagues in disseminating the concept of oral rehydration." The contribution of GML in this case was to facilitate a "technology transfer" to medical practice in the developed world.

Quality of Articles

OTA commissioned a review,* summarized here, of five currently active manuscripts and four recently published articles written by Gorgas staff members (the articles and manuscripts are listed in table 10). The articles are not necessarily a representative sample of the total GML output. They were selected by OTA to cover as diverse a group of topics as possible, subject to the practical constraint of what was available immediately. The review assessed the process of the research, including the adequacy of study design, extent of data collection, and methods of presenting the research findings. Presented below is an examination of the overall features which characterize the research reports, and assessment of the methods of presentation of the data.

Table 10.—Articles and Manuscripts Reviewed for the Office of Technology Assessment by Richard K. Riegelman, M.D., Ph. D.

Articles

1. Christensen, H., and DeVasquez, A. M., "The Tree-Buttress Biotope: A Pathobiocenose of *Leishmania braziliensis*," *American Journal of Tropical Medicine and Hygiene* 31(2):243-251, 1982.
2. Dietz, E., Galindo, P., and Johnson, K., "Eastern Equine Encephalomyelitis in Panama: The Epidemiology of the 1973 Epizootic," *American Journal of Tropical Medicine and Hygiene* 29(1):133-140, 1980.
3. Dietz, W., Peralta, P., and Johnson, K., "Ten Clinical Cases of Human Infection With Venezuelan Equine Encephalomyelitis Virus, Subtype I-D," *American Journal of Tropical Medicine and Hygiene* 29(2):329-334, 1979.
4. Young, M., Baerg, D., and Rossan, R., "Studies With Induced Malarias in *Aotus* Monkeys," *Institute Animal Sciences* 25(6):1131-1137, 1976.

Manuscripts

5. Petersen, J., "Identification of Phlebotomine Sand Flies (Diptera: Psychodidae) by Cellulose Acetate Electrophoresis" (in press).
6. Piesman, J., Sherlock, I., and Christensen, H., "Triatomine Density and Host Availability" (in press).
7. Seymour, C., Kramer, L., and Peralta, P., "Experimental St. Louis Encephalitis Virus Infection of Sloths and Cormorants" (in press).
8. Seymour, C., Peralta, P., and Montgomery, G., "Serologic Evidence of Natural Togavirus Infections in Panamanian Sloths and Other Vertebrates" (in press).
9. Seymour, C., Peralta, P., and Montgomery, G., "Viruses Isolated From Panamanian Sloths" (in press).

SOURCE: Office of Technology Assessment, 1983.

Overall Features of the Articles and Manuscripts

The articles and manuscripts reviewed reflect a wide spectrum of scientific activities. These activities include:

- study of a naturally occurring epidemic with potential for human transmission;
- development of new animal models for studying human disease;
- investigations of the mechanisms for transmission and reservoirs of disease in their natural field environment;
- laboratory investigations designed to assess the susceptibility of animal hosts as intermediaries in the transmission of human disease;
- reporting on a series of human cases of disease collected over more than 15 years;
- development of a new technique for performing enzymatic studies on disease vectors;
- field studies of the effect of a human living environment on the transmission of disease; and
- correlation of biochemical genetic characteristics of disease vectors with the epidemiology of disease.

Important features of these investigations include the ability to collect and coordinate data from a variety of sources. The ability of the investigators at GMI to bring together data from a variety of sources is demonstrated in these studies in at least the following ways.

- correlation of their laboratory investigations with findings from their field research and knowledge of the epidemiology and natural history of disease;
- cooperation with other laboratories, including CDC and a number of U.S. university, public health, and military programs;
- ability to respond to a naturally occurring epidemic, collecting data requiring cooperation with public health control programs, hospitals, and correlation with laboratory investigations; and
- ability to collect and test large numbers of disease vectors from a variety of natural environments.

The majority of the investigations represent unrelated studies. Three of the investigations how-

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*The review was carried out for OTA by Richard K. Riegelman, M.D., Ph. D., author of *Studying a Study; Testing a Test*, and a member of OTA's Health Program Advisory Committee. This section is based entirely on that review.

ever, include coordinated studies using two- and three-toed sloths found in the Panamanian forests.

These three studies reflect the ability of investigators at the laboratory to:

- collect a large spectrum of species of birds and mammals from a variety of natural environments;
- track the natural history of disease by placing radio transmitters on selected animals and recapturing them for sequential testing;
- perform viral isolation and serological testing needed to correlate with the epidemiology and natural history of disease found in the Panamanian forests;
- relate the field and laboratory findings to human disease potential; and
- use knowledge gained from earlier studies to improve the design and performance of subsequent studies.

Presentations of Data

Background and Hypotheses.—The authors frequently introduce their presentations by a succinct discussion of their study's purpose and its relationship to existing knowledge. These introductions are well referenced and place the studies in a context which does not require the reader to have a previous detailed knowledge of the field.

The study hypotheses are usually clearly stated and their relationship to previous studies are, on the whole, well outlined.

Study Methods.—The authors of the field laboratory studies provide detailed discussions of the location of their collections and the methods of preservation and preparation of their materials. The experimental studies provide an adequate description of the study methods, including references to the specific techniques employed. These presentations appear to fulfill the essential criteria that other investigators are provided adequate information to attempt to reproduce the findings.

When judgments as to technique and criteria for positive results are required the authors appropriately present the justifications for their choice. When the methods themselves possess limitations in their ability to measure the intended phenomena, the authors clearly identify these limitations.

Results.—The authors present the results of their studies in adequate detail. They consistently present and acknowledge their failures and the limitations of their results as well as presenting their positive findings. This practice should add to the value of these investigations by identifying areas for further research, appropriately limiting the conclusions, and preventing other investigators from pursuing unproductive approaches.

The statistical methods used in the articles require only basic methods. However, the methods used are appropriate and appear to be properly employed.

When interpreting the results of their studies the authors usually present a variety of potential explanations for their findings, including the explanation they favor.

In presenting their results, the authors generally are able to relate their findings to current scientific thinking as well as their implications for immediate disease prevention or control. The articles often suggest areas for further investigations.

Summary

In summary, the articles and manuscripts reviewed reflect a high level of expertise in designing and carrying out scientific research. The investigators demonstrate an ability to collect and coordinate data from a variety of sources, present data in an analytical manner, and build on and contribute to the worldwide scientific literature. The authors are able to take advantage of the unique features of their setting and experiments to contribute to knowledge of basic and applied biological science.

PEER REVIEW AT THE GORGAS MEMORIAL LABORATORY

One of the questions being addressed by the General Accounting Office (GAO) is about the peer review process at GML. Thus, this memorandum will not discuss peer review except for some comments on the relationship of peer review to the quality of research. By peer review, OTA is considering basically the process by which decisions are made to fund research projects with internal (core grant) money and the process of evaluating internal research. Research funded through grants and contracts is subject to peer review by the funding agencies, e.g., NIH and the World Health Organization (WHO). In those cases, GML is competing with other research organizations for support. In a sense, GML staff are competing with each other for core funds to support their projects that are not under grants or contracts. A peer review system for research proposals, and reviews of ongoing and completed work are mechanisms used to allocate resources according to merit and to assure that research quality is acceptable.

It is not uncommon for internal peer review systems to be less rigorous than externally funded systems. For instance, at NIH, researchers on the campus do not submit proposals through the same system that funds extramural research. Researchers within each institute do go through a formal process for allocation of intramural research funds, but review is basically within the institute itself. Proposals and protocols are not scrutinized by outside experts, but, at specified intervals outsiders do evaluate the work that goes on within institutes.

OTA gained some insight into the peer review process at GML through the telephone survey about Gorgas. There was a general lack of agreement about whether a peer review process—either to review research proposals, protocols, or results—does in fact exist. It is clear that even if a process has been set up on paper, it does not function effectively on a regular basis.

The fact that GML does not seem to have a well-known system for allocating money within the organization is something that requires consideration in future plans. A truly internal system, such as NIH uses, may not be the best plan for GML. Institutes in NIH have a large core of individuals with knowledge in a specific field. For instance, all researchers at the National Cancer Institute are knowledgable about some aspect of cancer. There is a large number of people there to provide adequate review of internal research proposals.

At GML, investigators are unique in education, training, and research areas. It would probably be difficult and perhaps not so effective to have only GML staff review each other's proposals and research results, though that is also desirable. The main peer review body could be drawn from the Advisory Scientific Board, which has good scientific representation from the relevant disciplines. A model for how such a group might operate is the peer review process of the Plum Island (New York) Animal Disease Center of the U.S. Department of Agriculture. In that case, there are five non-Government consultants who visit once each year (but may be called to visit in the interim if necessary). The consultants are selected by the laboratory director and are responsible directly to that person. The consultants produce a report assessing all programs. The consultants' expenses for the visit are paid (98). Paying for travel is even more critical for GML, since travel to Panama is relatively expensive.

GRANTS AND CONTRACTS

The record of an institution or a researcher can be measured in the number and dollar value of grants and contracts awarded from external sources. Externally funded projects are more likely to undergo vigorous peer review than are those funded internally by an institution. (See "Peer Review at the Gorgas Memorial Laboratory," above.) This is a particularly appropriate measure for researchers in the United States, where there is a relatively large amount of money available for research, though competition is quite keen.

Most of the research at GML is funded through the core grant, rather than through competitive grants and contracts. Addressing this, the 1980 Fogarty Site Visit Report states:

> In these times of financial constraint everywhere, the Team does not feel that too many expectations should be held out that project grants and contracts could or even should supplant the necessity for the maintenance of adequate core support.

A number of past and current projects have received grant or contract funding from sources other than the core grant, including the WHO Special Programme for Research and Training in Tropical Diseases (see app. A), the U.S. Army and Navy, NIH, and private foundations. Table 11 lists current, completed, newly approved, and pending grants and contracts. There are some grants and contracts in every GML program.

Table 11.—Gorgas Memorial Laboratory: Grants and Contracts as of July 1983

Current grants:
U.S. Army Drug Evaluation Contract
U.S. Navy Training Project
WHO/TDR Triatomine Blood Meal Contract
WHO Clinical Trial for Evaluation of Leishmaniasis Therapy
WHO Isozyme Lutzomyia—Sand Flies
NIH/Yale Arbovirus—Yellow Fever
WHO/TDR Chagas' Disease
UNDP/World Bank/WHO Leishmaniasis in Honduras

Completed and or terminated[a] grants/contracts:
Tabasara Hydroelectric Environmental Impact Study
NIH/NCI Cervical Cancer Study
NIH/NIAID Epidemiology of St. Louis Encephalitis
AID *In Vitro* Malaria Culture
WHO/TDR Control of Simuliids

Approved contracts:
Panamanian Ministry of Health/Interamerican Development Bank—Malaria and Leishmaniasis
NIH/NCI Epidemiology of Human T-Cell Lymphoma Virus
WHO/PAHO Epidemiology of Childhood Respiratory Illnesses in Panama

Pending grants:
Rapid Early Serodiagnosis of Leptospirosis by Detection of Antigen in Body Fluids of Infected Persons
Epidemiologic Assessment of Preventable Illness in Honduran Refugee Camps
Effects of Two Arbovirus in the Development of Panama
Regional Reference Center for Studies on New World Phlebotomine Sand Fly Host Feeding Patterns

[a] Usually because of lack of funding.

SOURCE: Gorgas Memorial Laboratory, Office of the Director, July 1983.

The fact that GML has competed successfully for research money is evidence that the quality of research is equal to other research projects funded by those agencies at other institutions. Support for new projects by these funding bodies is also dependent on successful past performance, giving some assurance that GML is considered dependable. An official at the National Cancer Institute (32) was very positive about Gorgas' ability to carry out a newly approved epidemiologic study involving human T-cell lymphoma virus, based on their past work. He also mentioned that GML is the obvious choice as a coordinating center for a possible future collaborative study of cervical cancer in several countries in the region.

Quality of Research at GML as Seen by Experts

Several questions in the telephone survey that was commissioned for this technical memorandum (see app. D for a more detailed discussion of the survey results) addressed the quality of research and training at GML. In response to a general question, "How would you rate the work of GML?" most of the 23 experts interviewed reacted positively. Some programs were rated excellent, including the work in virology (especially in arboviruses), malaria, medical entomology, trypanosomiasis and leishmaniasis, cancer, STDs, and environmental studies. Other programs, bacteriology, for instance, were rated lower.

A commonly held sentiment was that the quality of work varies from program to program, with many strong points and some weak points, but that such a state of affairs was to be expected in an institution that has been in existence for so long. In some areas the work has become routine, with slow but steady progress. Some work was described as not very original, but, technically good. Presumably this refers to such activities as serotyping of viruses, which is of public health importance, and is done routinely at GML, but is not necessarily innovative.

Several people made the point that judgments about quality of research must be tempered by consideration of the conditions under which work is done—field conditions make for a much different situation than that encountered at NIH. Particularly in light of working conditions in the Tropics, GML was rated highly.

The uncertainty of financial support affects the quality of research, according to a number of experts. Lacking a secure future, it is difficult to attract top scientists to work at any institution. In addition, the researchers already there are hampered in planning for all but the most immediate research.

There was a diversity of opinion about whether the quality of research at GML has changed appreciably over the years. Research emphases have changed and the whole field of scientific research has changed so greatly that such a judgment is difficult to make. Of those who did answer, some felt there was no change, others a change for the better (variously since World War II, to within the last 1½ years). A number noted a general decline in research quality over the years, all of those respondents relating the decline to uncertain funding.

The experts contacted were asked about the quality of tropical medicine training offered at GML. Most gave it a high rating. The unique setting was considered the most important asset in the training programs. The opportunities for clinical experience were particularly important for the military. In this regard two respondents referred to a comment of General Douglas MacArthur's that in the Philippines he needed three divisions to do the work of one, since two would be in the hospital with malaria or dengue. The disease ecology is such in Panama that similar opportunities for learning about tropical diseases do not exist in many other places. One expert mentioned that training in Puerto Rico, for instance, would not be as valuable as that at GML. A few people said that the training had gone downhill during the past few years because of financial constraints.

Summary

The research carried out at GML over the years has been of generally high quality. OTA's analysis, the survey of expert opinion, the critical review of articles and manuscripts, and past site visits are all in agreement on this general conclusion. As is the case in any institution with a long history, there are strengths and weaknesses. Research emphases have shifted over the years, and the quality has varied as well. The results of the telephone survey confirm that most of the major programs are strong and of good quality, and that there are fewer weak points.

However, mechanisms to assure continued high quality of research are not in evidence. There is a lack of an effective peer review process for allocating money to research projects funded by the core grant. While grants and contracts funded externally have passed through a competitive process designed to assure high quality, internally generated and funded projects do not necessarily receive the same degree of scrutiny. Another example of a potential problem area is collaboration with other high-quality institutions. GML must become more aggressive in seeking and in strengthening interaction and collaboration with scientists and institutions from other countries (especially the United States). And, as mentioned, GML could make a larger effort to publish study results.

OTA finds that GML is carrying out research of high quality, and that the institution enjoys a generally solid reputation in the field of tropical medicine research. The most serious threat to maintaining good research is continuing uncertainty about future financial support.

Chapter 4

Relevance of Research at Gorgas Memorial Laboratory to Health Problems in Tropical America

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This technical memorandum considers the term tropical diseases to refer both to those classically defined as tropical diseases, such as schistosomiasis, and to those in a broader definition of the term, such as tuberculosis and malnutrition (see ch. 1). Socioeconomic status (e.g., malnutrition, poverty) defines the Tropics and, to a very large degree, tropical diseases. Otherwise life in urbanized tropical America presents the same hazards to health as life in North America or Europe. The intimate relationship between health status and economic and social progress means that some health problems in tropical America will only succumb to long-term socioeconomic advancement, yet tropical diseases, by their enormous impact on health status, simultaneously and seriously affect the economies of tropical countries. The six tropical diseases singled out by the World Health Organization (WHO) for special programmatic research support—malaria, schistosomiasis, filariasis, trypanosomiasis, leishmaniasis, and leprosy—together affect between 700 million to 800 million people. The first three each affect more than 200 million people worldwide (5).

The resulting amount of human suffering and disability is enormous. This argues for urgent humanitarian action where feasible interventions exist. Significant costs are involved in treating such diseases and in implementing public health programs for their prevention and diagnosis, even though health services are usually underfunded and inadequate in most of the less developed countries. However, the most substantial economic impacts may be the indirect ones affecting a country's human resources and productivity.

Health problems in the region of tropical America cover a broad range because of the great variations in climate, geography, socioeconomic conditions, and culture. Modernization, population growth, and rapid rural-to-urban migration cause many diseases of the developed world to have growing significance in tropical and developing America, especially among affluent, middle-aged, and urbanized persons. For example, heart disease, stroke, diabetes, cancers, and accidental injuries are all emerging as major causes of morbidity and mortality in statistics for the Latin American and Caribbean regions.*

Even as diseases of the developed world acquire increasing importance as major causes of mortality in tropical America, the nonfatal diseases caused by parasitic and infectious agents remain a critical drag on developmental progress and the quality of life. Furthermore, in the developing countries, life expectancy at birth is much lower than in the developed world. This is a direct result of high infant and childhood mortality. The major killers of infants and children are three groups of diseases: diarrheal and enteric infections (fecal-borne), respiratory infections and measles, and malnutrition.

This chapter will first describe some of the major tropical diseases and conditions of ill-health of tropical America. Following that, the Gorgas Memorial Laboratory's (GML) research and related activities will be discussed in light of the information on regional health problems and research needs.

Evaluation of research relevance quickly becomes subjective. Research by its nature is open-ended. If science administrators and researchers could predetermine all lines of productive research, they would do so. The reality is often a simpler hope—for good judgment and good luck.

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*Caution is necessary, however, in interpreting these statistics, because they derive from health care systems that are weighted (because of the training of physicians, the availability of health facilities, the logistical problems of data collection, etc.) towards the diagnosis and recording of acute, traumatic, or degenerative disease presentations in urban areas.

In evaluating the relevance of research at GML, OTA depended on identified health problems and needs, resulting research questions and opportunities, and the relationship of GML's research to those health problems and research needs.

TROPICAL DISEASES: DESCRIPTION AND STATUS

Acute Respiratory Infections

Acute respiratory infections (ARI) are a major cause of mortality in children under 5 and the elderly. The group includes many viral and bacterial infections: influenza (myxoviruses, type A, B, C), parainfluenza (paramyxoviruses), measles (paramyxovirus), respiratory syncytial viruses, adenoviruses, rhinoviruses, *Streptococcus pneumonia* and other bacteria, chlamydia (congenital), and mycoplasma. Influenza and pneumonia are among the top five causes of death in children under 5 in every country of the Pan American Health Organization (PAHO) region (75). In addition to the serious mortality risk for the very young and the very old, these infections are a tremendous social burden in terms of work productivity lost and demands on the health care system by all age groups.

These infections are aggravated in conditions of malnutrition and substandard living conditions, and in combination with other infectious diseases. A principal epidemiological factor of ARI transmission is close, overcrowded associations that promote inhalation of aerosolized pathogens by coughs, sneezes, and personal contact.

For most of these diseases there is no treatment other than symptomatic and supportive relief, though bacterial infection can be effectively treated with antibiotics. Vaccinations for measles, whooping cough, and diphtheria are feasible and promoted under the Expanded Program on Immunization of WHO. Vaccines against influenza and pneumococcal pneumonia are available but have reduced usefulness in developing countries: Pneumococcal vaccine is not very effective in children under 2 years old; influenza vaccines must be renewed periodically according to the currently prevalent strain.

Improved access to health care is a critical factor, but also needed are field-based epidemiological studies. ARI control is largely ignored in most developing countries. This is a function of difficult diagnosis (of the etiologic agent), lack of effective treatment, lack of definition as a tropical disease, and as an entity worthy of focused research. Longitudinal studies on the epidemiology of ARI using rapid diagnostic techniques are needed. These studies could simplify the prevention and treatment of ARI by precisely identifying the important etiologic agents in geographic areas and by determining the risk factors which make ARI mortality so high. Practical management of ARI depends on differential diagnosis of viral from other bacterial, chlamydial, and mycoplasmal agents for which specific treatments are effective. With risk factors defined, intervention against them could be initiated. At the same time, such studies would produce baseline prevalence data for subsequent evaluation of intervention measures taken.

Diarrheal and Enteric Diseases

Diarrheal diseases are the leading cause of death in children under 5 years of age in over half the countries of Latin America and one of the top five for all other countries. Data from several countries indicate that the typical child below 5 years of age experiences four to eight diarrheal episodes annually. In some countries, up to 45 percent of all hospital visits during the months of highest diarrhea prevalence are due to childhood diarrhea, and case fatality rates as high as 40 percent have been recorded (76).

A comparison of death rates in children under 1 year of age is startling. For North America (United States and Canada), the mortality rate in infants in 1979 was 21.9 per 100,000; for Latin America it was 914.6 per 100,000, 40 times higher, almost 1 in 100 infants dying of diarrheal disease. Because underreporting from rural areas is still a problem, it is likely that the statistical number of diarrheal cases will increase as health services are extended to rural populations.

Diarrheal diseases constitute a clinical syndrome of varied etiology, all of which are transmitted by human feces. These include bacilli, viruses, and parasitic and helminthic parasites, such as shigellae, salmonellae, *Escherichia coli, Campylobacter, Yersinia,* rotaviruses, amoeba, giardia, ascaris, and ancylostoma. Poliomyelitis is also a fecal-borne disease.

Rotaviruses, which in recent years have been found responsible for almost half of infant diarrheas in the developing world, were first detected in humans in 1973. Serologic studies have shown that by the age of 2 years, nearly all children have had the infection. A Guatemalan community study indicated that rotavirus accounted for 10 to 20 percent of all diarrhea there.

Escherichia coli is a second important cause worldwide of diarrheal disease. Only certain strains which are classified in three groups cause disease: enterotoxigenic *E. coli,* enteroinvasive *E. coli,* and enteropathogenic *E. coli.* Each group has a distinctive physiological and pathological symptomatology. Serotyping based on bacterial cell wall antigens is a second classification system.

Other important diarrheal pathogens are *Shigellae, Salmonellae* (both typhoid and nontyphoid), *Campylobacter, Entamoeba histolytica* (amebiasis), and *Giardia lamblia* (giardiasis).

Although acute diarrheal diseases remain a leading cause of childhood morbidity and mortality in most of the Americas, prospects for their control are steadily improving. Intensive research in recent years into almost all aspects of diarrheal disease has led to a number of breakthroughs and technical innovations, such as oral rehydration therapy (ORT), which has become the main strategy of the WHO/PAHO diarrheal disease control program. Therapeutic studies continue to document the effectiveness of this simple, safe method which uses a single specific orally administered water solution of electrolytes and glucose. An ORT trial project begun in 1978 in Costa Rica has proved an effective lifesaver in both bacterial and rotaviral infant diarrhea (70,72,83). A recent study (95) demonstrated that even in well-nourished children in developed countries, ORT is a safe and effective treatment for acute diarrhea (regardless of etiologic agent) and could replace the use of intravenous fluids in the majority of such children.

In addition to ORT, four other major strategies comprise the diarrheal disease control program: 1) improved child care practices, including promotion of breastfeeding, proper weaning, and personal hygiene; 2) health education; 3) improved water supply, environmental sanitation, and food hygiene; and 4) epidemiologic surveillance. A medium- to long-term objective is to integrate diarrheal disease activities into existing primary health care systems.

With the growing evidence of rotavirus importance in diarrheal disease, further epidemiologic, clinical, and basic research is needed. A major objective now is to develop a vaccine for humans. Such a vaccine exists for animals. Immunological diagnostic testing exists which can be utilized for field studies of prevalence and incidence in geographic localities.

Childhood mortality is the highly visible tragic aspect of enteric disease, but the chronic and debilitating effects of these parasitic and infectious diseases (e.g., chronic anemia due to intestinal hookworm) rob a nation of productivity, vitality, and initiative. WHO estimates there are at least 650 million people in the world with roundworm (ascariasis), 450 million people with hookworm (ancylostomiasis), 350 million people with amoebiasis, and 350 million people with whipworm (trichuriasis) (99). Fecal-oral transmission is the common denominator of all these diseases. Lack of safe and adequate water supply and of proper excreta disposal, two of humankind's most basic needs, are the critical deficiencies that promote these diseases. In rural Latin America, 68 percent of the population lack access to water supply service, and 98 percent lack sewage service of any type. In urban areas, 22 percent lack access to water supply service, and 57 percent have no sewage service.

Malnutrition

Malnutrition is a primary cause of death of children under 5 years of age in Latin America. Though not a disease per se, it is so intimately involved in disease processes and ill-health to warrant specific mention in this overview. The Inter-

American Investigation of Mortality in Childhood showed that low birth-weight (2,500 g or less) and nutritional deficiency were the direct cause of 6 percent of deaths before age 5 and an associated cause in 57 percent of all deaths (85). Death is the final outcome in a chain of events that begins before birth and then involves the pernicious interaction of malnutrition and infectious disease. Maternal malnutrition (together with maternal age and parity, two other determinants in infant mortality (86)); produces premature birth and low weight at birth, both serious risk factors for the newborn. Infants who survive the neonatal period tend to thrive for the first 6 months of maternal feeding, but then come to risk from varying degrees of kwashiorkor and marasmus, the two poles of protein-energy malnutrition. According to Gueri (48), in a great majority of cases the problem results not from lack of food in the home but rather from maldistribution of food within the household, from lack of knowledge about child feeding, from an unsanitary physical environment conducive to infectious diseases (particularly gastroenteritis) that increase the child's energy requirements while decreasing its appetite, from early replacement of breastfeeding with highly diluted and contaminated milk formulas, and in some cases from sheer neglect.

Though malnutrition as a primary cause of morbidity and mortality is less prevalent in adolescents and adults, it still must be considered a major contributing factor in infectious diseases. Immunologic defense mechanisms are seriously compromised by malnutrition. The synergistic interaction of malnutrition and disease is well documented. For example, Scrimshaw, Taylor and Gordon (101) observed that, except where populations are malnourished, or otherwise uncommonly susceptible to disease, the incidence of tuberculosis is significantly lower than would be expected by the widespread presence of the tubercule baccilus. Mortality due to measles was 274 times higher in Ecuador than in the United States in 1960-61, a time before the development of immunization to the disease (85). Thus in all analysis of tropical health problems, protein-energy malnutrition must be considered a contributing cause in the disease process, and as a primary cause in children under 5 years old.

Important research and intervention experiments have been carried out under the auspices of PAHO. The principal research centers are the Institute of Nutrition of Central America and Panama (INCAP), the Caribbean Food and Nutrition Institute (CFNI), and the Latin American Center for Perinatology and Human Development.

Malaria

Malaria is a disease caused by a protozoan blood parasite transmitted by various anopheline species of mosquitoes. It is one of the most widespread and destructive diseases in the world and has made a resurgence in the last decade with a more than two-fold increase in world prevalence (127,128). The incidence of malaria in developed nations, such as England and the United States, has also been increasing due to imported cases. Estimated malaria incidence worldwide is 300 million cases per year. In 1982, 702,000 confirmed cases were reported from the Americas. These statistics are large but undoubtedly underreported, because the disease is contracted in rural areas remote from medical facilities. An estimated 64.9 million people live in areas of tropical America where the risk of contracting malaria persists. The countries of worst malaria incidence are Haiti, Guatemala, Honduras, El Salvador, Colombia, Bolivia, and Brazil.

The resurgence of malaria in the last decade is a setback due to the failure of the global eradication campaign based on DDT house-spraying and supplementary mass drug distributions. Early successes led to overconfidence that ignored the complexity of a disease caused by four different species of parasite and transmitted by many different species of mosquito vectors, each with peculiar behavior patterns in widely varying ecological and sociological settings. The serious consequences of that failure are insecticide-resistant mosquito vectors and drug-resistant strains of the parasite.

Malaria research is in a new period of vigorous activity, like most of parasitology. Molecular biologists, geneticists, and biochemists have begun to apply their research skills to the many important questions that were ignored during the eradication era. Metabolic studies can identify parasite-specific enzyme pathways that can be exploited to kill the parasite without harming the human host. Membrane research can reveal how the parasite finds, attaches to, and invades red blood cells yielding important clues for drug therapy and vaccine research. Recent clinical studies have suggested better ways of preventing and treating cerebral malaria, an often fatal complication of severe malaria infection.

The spread of drug-resistant malaria (by the species *Plasmodium falciparum*) is of great concern worldwide. Regular monitoring of local parasite strains is necessary to keep abreast of therapeutic changes that may be needed, both in type of drug and dose. In Latin America, serious drug-resistance has still not moved north of the Panama Canal. Renewed effort to develop new drugs is producing results, but takes years to move from laboratory screening through animal testing to human trials.

Vector biology studies are critical to any rational mosquito-control effort. Cytogenetic research which analyzes insect chromosomes has identified species complexes that were previously unrecognized by conventional taxonomy. As an example, *Anopheles gambiae,* the notorious malaria vector in Africa, is now known to be a complex of several distinct species all identical to the unaided eye. Cytogenetic differentiation of the various species has explained the different behavior patterns of the *A. gambiae* complex and defined the important vector species. Research on physiological resistance mechanisms can aid the development of better insecticide methods. Behavioral resistance, the avoidance of insecticides by insects, is important for two opposite reasons—the killing effect is reduced, but transmission may still be interrupted, if vectors avoid human habitations.

Field- and community-based studies are needed to assess the impact of antimalaria interventions. The ecological impact of vector intervention is critically important. The selection of insecticide-resistant vectors has seriously handicapped current control efforts. The effect of antimalarial activities on population immunity levels still needs clarification. Studies in the past have clearly documented the immediate impact of antimalarial projects on morbidity and mortality, but not the long-term consequences when projects cease or fail. Other studies need to evaluate the importance of sociological and human behavioral factors and the usefulness of health education, community self-help, and volunteer collaborators.

Significant progress is being made on the development of a vaccine against malaria, including the identification of surface antigens and their production by bacteria. If animal testing confirms the feasibility of immunization against this parasite, extensive human and field trials will be required, before there is widespread usage of vaccines in the control of this disease. The wide usefulness of a vaccine is also debated considering the many difficulties associated with implementing other disease immunization campaigns.

Chagas' Disease

Chagas' disease (American trypanosomiasis) is caused by a protozoan parasite of the blood and tissues and transmitted by reduviid bugs ("cone-nosed" or "kissing" bugs), common blood-sucking insects in the Americas. It is a disease of poor rural areas with substandard housing that provides harboring sites for the bugs to live and breed. About 150 species of mammals have been incriminated as reservoir hosts, including dogs, cats, guinea pigs, rats, opossums, and other rodents and marsupials. The parasite has two life stages in the mammalian host, one that circulates in the blood and another that proliferates intracellularly in tissues.

In 1974, WHO estimated that out of 50 million exposed, a total of 10 million persons were infected with the Chagas' disease parasite *Trypanosoma cruzi* (discovered by Carlos Chagas of Brazil). Studies in Brazil have shown Chagas' disease to be a significant cause of mortality in those under 45 years of age (84) and a heavy social burden due to high rates of hospitalization (with unsatisfactory outcome) and disability assistance (78).

After initial infection by the reduviid bug, the acute phase of the disease varies in severity according to age. Cardiac arrhythmias, myocardial insufficiency and collapse, or central nervous system damage may result in death. The younger the individual, the greater the severity. Mortality is high in children under 2 years of age, while adults may show no symptoms. The acute stage may resolve completely in a few weeks or months, or may pass into a subacute or chronic stage. There is no effective cure. Long-term sequelae are cardiomyopathy leading to heart failure and grotesque enlargement of the digestive tract (megaesophagus and megacolon).

The transmission threat in rural areas is great, but transmission by blood transfusion is also a major problem for blood banks in Latin America.

The disease is found in every country of the Western Hemisphere, except Canada and the Caribbean. Opossums and other mammals harbor the disease in the Southern United States, and a small number of indigenous human cases have occurred in recent years (e.g., two in California in 1982).

Control measures concentrate on insecticide spraying of houses and upgrading of housing construction (adobe, mud, cane, thatch, or otherwise poorly constructed rural homes with cracks in the walls are the usual harborage of the insect vector).

An effective drug cure is a critical research need. With a therapeutic drug in hand, a simple effective test for early diagnosis would be essential—the long-term effects once they appear are irreversible. Vaccine research is underway, but this disease has a complicating factor—the long-term pathology seems to result from the body's immune response reacting against the parasite and cross-reacting to its own heart and nerve tissue. Vector bionomics remain important research topics for defining transmission areas, vector behavioral characteristics, and improved control measures.

Leishmaniasis

Leishmaniasis is a disease with three clinical presentations depending on the leishamanial parasite species. In each case, the protozoan parasite species is transmitted by bloodsucking phlebotomine sandflies. Cutaneous leishmaniasis is a self-limiting and usually self-resolving sore at the point of infection. Mucocutaneous leishmaniasis is caused by a different *Leishmania* species that begins as a sore but commonly metastasizes and proliferates in the nasal and pharyngeal mucous membranes. Gross destructive disfigurement of the nasal passages occurs. Visceral leishmaniasis (kala-azar) is a third type of disease in which spleen, liver, bone marrow, and lymph glands are the sites of parasite proliferation. Fatal outcome in children is common.

The disease exists in all Latin American countries except Chile, and in some the number of cases is increasing because of agricultural colonization in jungle areas. In the late 1970's, cutaneous leishmaniasis seriously impeded a Bolivian scheme to relocate people outside the overcrowded *altiplano*. Many of the colonists abandoned their land. More than 60 percent of those who did said that leishmaniasis was their reason for returning to the mountains. It has also significantly hampered both oil exploration and roadbuilding in several Andean countries (76).

Epidemiologically, most forms of the disease are transmitted to humans from animals in the jungle (zoonoses), representing a health hazard to anyone working there, and rendering control unsatisfactory or impracticable.

Specific treatment is now limited to antimony compounds that are not always effective and often have adverse toxic side-effects. Another disadvantage is that they require daily injections over 10 to 20 days, which makes them impractical for patients living in remote and inaccessible areas. Hospitalization for such a period is not only expensive but also a major inconvenience to the patient who cannot afford to leave work or farm for an extended period. For these reasons, improved treatment of the tens of thousands of existing cases is a priority research goal. PAHO/WHO currently has a structured effort to develop new therapeutic drugs. Allopurinol is a promising compound of current research activity (119).

In other PAHO investigations of leishmaniasis epidemiology, a seroepidemiologic survey in Panama revealed an apparent focus of leishmaniasis transmission without clinical infection. Completely subclinical leishmaniasis was previously unknown and may be important to vaccine development. Rapid species diagnosis of leishmanial sores may be soon possible by a recently published technique of DNA hybridization (124).

This would permit early treatment of the destructive mucocutaneous form of the disease, as well as facilitate precise epidemiologic field studies.

Arthropod-Borne Viral Diseases (Arboviruses)

This large group of diseases is caused by viruses (currently about 80 in humans) defined by ecological, epidemiological, and clinical parameters. Strictly speaking, arboviruses replicate in and are transmitted by arthropods (predominantly mosquitoes, but also ticks, sandflies, midges and gnats). There are some arbovirus- like diseases whose vector is still unidentified and some whose early epidemiological profile incorrectly suggested arthropod transmission; their symptoms (e.g., Argentinian and Bolivian hemorrhagic fevers) must be differentiated from those of true arboviruses. The number of arboviruses is growing rapidly as research resolves the etiologic agent of many fevers and brain inflammations (encephalitis) of unknown origin and elucidates transmission cycles. Examples of arboviruses include: yellow fever, dengue fever, eastern equine encephalitis (EEE), western equine encephalitis (WEE), St. Louis encephalitis (SLE), Venezuelan equine encephalitis (VEE), California encephalitis (CE), Colorado tick fever, Chagres fever, and Oropouche fever. (Locality names denote the source of first isolation; range of each is far wider.)

Clinically these diseases are classed in four groups (6): 1) acute central nervous system disease usually with inflammation of the brain (encephalitis), ranging in severity from mild aseptic meningitis to coma, paralysis, and death (WEE, EEE, CE/LaCrosse encephalitis, SLE); 2) acute benign fevers of short duration, many resembling dengue with and without a rash (exanthem), although on occasion some may give rise to a more serious illness with central nervous system involvement or hemorrhage (yellow fever, dengue, VEE, Oropouche); 3) hemorrhagic fevers, including complications of acute febrile diseases (previous group), with extensive hemorrhagic involvement, frequently serious, and associated with shock and high-fatality rates. One of them, yellow fever, also causes liver damage and jaundice; 4) polyarthritis and rash, usually without fever and of variable duration, benign, or with arthralgic sequelae lasting several weeks to months.

Most of these infections are diseases of animals (zoonoses) accidentally transmitted to man, though epidemics can occur with man; the principal source of vector infection. In 1981, an epidemic of dengue fever swept through Cuba with 344,208 cases and 158 deaths. The 1977-80 pandemic of dengue in the Caribbean and Central America caused a half-million cases.

Laboratory diagnosis can identify arboviruses and define antigenically similar groups, but great geographic and climatic diversity is found in each serologic grouping. This emphasizes the complexity and challenge of arbovirus research and control. There is no cure for these diseases, only symptomatic and supportive relief. Early diagnosis of serotype has three important values: to differentiate ambiguous presenting symptoms; to anticipate life-threatening complications, as in yellow fever and dengue fever; and to target the type of vector which then determines control strategies. Current control efforts rely on identifying epidemic outbreaks early in order to institute vector-control measures such as insecticide fogging. However, disease surveillance is not well developed in many tropical countries of the region.

Only yellow fever has an effective vaccine. There are experimental vaccines for certain strains of dengue fever, VEE, and WEE. The general utility of arbovirus vaccination is doubtful, though, because of the complexity involved. The wide variety of arboviruses, most occurring only sporadically in humans, and without inducing cross-immunity, raise many questions about implementation and bring the realization that vaccination is unlikely to be a panacea. Vector control will remain the primary intervention method. Entomologic research on vector bionomics together with surveillance of sentinel populations (animal reservoirs and vectors) are activities for emphasis. Especially important is elucidation of the vector-bridge concept—the factors permitting transmission of these zoonoses to humans when the principal vector arthropod is not a human-biter.

Yellow fever was the first arbovirus disease of the Tropics to be recognized and elucidated. It was William Gorgas who eradicated the disease from the Panama Canal Zone and Cuba in the early 1900's. Further success was recorded throughout Latin America against urban yellow fever, such that no cases were documented in the Americas for the past four decades. Jungle yellow fever, however, remains a major threat in tropical America. It is the same virus maintained by transmission through a number of jungle mosquitoes with monkeys and possibly certain marsupials serving as reservoirs. Recent research has demonstrated that transovarial transmission (passage of the virus from the female mosquito to the egg) occurs in vectors of yellow fever (26) (and other arboviruses). Thus, the mosquito may function not only as a vector, but also as a reservoir. Human cases are associated with man invading the jungle habitat. In recent years, however, an outbreak in Colombia appeared where there were no apparent known vectors or reservoirs and in Trinidad where no cases had been detected for almost 20 years. The possibility of unknown reservoirs or vectors is of concern. *Aedes aegypti* the vector of urban yellow fever remains abundant throughout the hemisphere (including the United States), posing a persistent threat of epidemic outbreaks in large population centers.

The disease occurs in periodic cycles stretching over several years which depend on the buildup of nonimmune individuals in a population who are then swept by an epizootic of the virus leaving an immune population of survivors.

Vaccination of human populations near endemic jungle areas is one strategy. Surveillance of monkey populations and jungle mosquitoes by sampling for virus isolation is an important control measure that gives early warning to institute remedial action.

Dengue fever is a disease caused by four different serotypes of the dengue flavivirus. In recent years large epidemics of this virus have swept the Caribbean and Central America. In 1981, the first indigenous cases in the United States since the 1940's occurred. The virus is endemic in the Caribbean and is transmitted by mosquitoes of the genus *Aedes,* including the common urban vector *Aedes aegypti* which is found as far north as St. Louis, Mo. It breeds in small containers of water such as discarded tires, cans, and jars. A serious, sometimes fatal, complication of dengue fever is dengue haemorrhagic fever (or dengue shock syndrome).

Oropouche fever is emerging as a very important type of arbovirus disease, because of its debilitating symptoms that reduce productivity due to convalesence. The virus is transmitted by biting midges (*Culicoides* spp.) in urban and periurban areas. There is probably also a silent transmission cycle in forested areas.

Filariasis

Several species of filarial nematode worms can inhabit the skin, other tissues, or the lymphatic system causing disease in humans. These parasites are transmitted by bloodsucking insects. In Latin America only two worms are considered public health problems, *Wuchereria bancrofti* and *Onchocerca volvulus.*

The bancroftian filariasis was introduced from Africa. It is transmitted by several species of mosquitoes including common household pest species. The adult worms live in the lymphatic system and cause pathology depending on the immune response of the host. Inflammation and gross obstruction results in varying degrees of swelling of the lymph glands up to frank elephantiasis of the legs, breasts, or scrotum. Adult worms release immature forms (microfilariae) that circulate in the blood which then infect feeding mosquitoes to complete the transmission cycle. Chemotherapy and vector control are currently imperfect and need more research.

Onchocerciasis is also known as river blindness, because the blackflies (*Simulium* spp.) that transmit it live and breed in or near waterways. The disease occurs in well-defined parts of Africa and in the Americas, in discrete foci in Guatemala, Brazil, Colombia, Ecuador, Mexico, and Venezuela. Ecuador's onchocerciasis focus was only discovered in 1980. A Panamanian blackfly has recently been shown to be a potential vector of *O. volvulus.*

The adult worm lives in the tissues of the body and often forms large nodules where an intertwined clump of worms localizes. Microfilariae released by the adults migrate through the body in the subcutaneous tissues where they can be picked up by feeding black flies. If microfilariae reach the eye, lesions and blindness can result. Control measures focus on vector control and blindness prevention (imperfectly achieved by chemotherapy and nodule removal).

Schistosomiasis

This debilitating disease is caused by a fluke. The worm-like adult parasite lives in the human host's bloodstream. Eggs are deposited in the blood vessels and escape into the bowel or bladder, or lodge in other organs, where they produce inflammation and scars. The complex lifecycle involves excretion of the eggs into water sources, an intermediate snail host in which proliferation occurs, and an immature stage that can penetrate the unbroken skin of persons who enter infected water. Three major species of the fluke occur worldwide, only one in the Americas, *Schistosoma mansoni,* which was introduced from Africa.

S. mansoni is now established in suitable snail hosts in more than half the States of Brazil, where 10 million people are believed infected, in Surinam, where 10,000 people are probably infected, and in parts of Venezuela, where 10,000 more people are thought to have the infection. Foci in the Caribbean occur in the Dominican Republic, Guadeloupe, Martinique, and St. Martin. A few cases have been detected in Montserrat. The disease is declining in Puerto Rico and Saint Lucia due to intervention measures (76).

Chemotherapy against the disease is effective and relatively safe. Total and complete coverage in endemic areas can be difficult to achieve requiring other measures to complement control efforts, particularly attention to water and excreta sanitation and anti-snail treatment of breeding sites (mollusciciding against the snail host).

Schistosomiasis is spreading worldwide due to water impoundment and irrigation projects which create and expand suitable environmental conditions for snail hosts and increase human-snail contact. Areas where large hydroelectric dams are being built especially in South America deserve special surveillance and assessment.

Leprosy

Leprosy is a chronic bacterial disease that continues to be an important public health problem in the Caribbean and Latin America. A quarter-million cases are registered in the region, perhaps twice that number are prevalent. As case-finding and notification improved, reported incidence increased with extension of anti-leprosy efforts. Depending on the host's immunologic response, leprosy can range from the benign tuberculoid form with localized skin lesions and some nerve involvement to the malign lepromatous form that causes spreading lesions which become nodular and disfiguring, destruction of the nose, involvement of the vocal cords and eyes, and severe nerve damage. Over half the cases in Latin America are the lepromatous form.

Research on the epidemiology of leprosy is still needed. A number of useful drugs are now available for treatment. Drug-resistant strains of *Mycobacterium leprae* have resulted in recommendations for combination chemotherapy which will shorten the treatment period. If organized and administered well, this will lighten the workload of health services, improve patient compliance, and result in better prognosis. Vaccination against the disease is in human trials but still years from routine use. The PAHO-associated Pan American Center for Research and Training in Leprosy and Tropical Diseases (CEPIALET) in Caracas, Venezuela, carries out a full research agenda on leprosy, as does the U.S. Public Health Service in Carville, La. Other philanthropic institutions provide support to leprosy control either directly to the countries or through PAHO.

Tuberculosis

Tuberculosis is a mycobacterial disease transmitted mainly by airborne droplets. The lungs are first involved, after which infection can spread to all parts of the body. Though the disease is decreasing slowly in the Americas, it is still a serious problem in most countries of the region.

Even countries such as Canada and the United States, with highly developed coverage for diagnosis and treatment, have significant numbers due to immigrants from tuberculosis-prevalent areas.

Control methods based on BCG (bacille Calmette-Guerin) vaccination, diagnosis from those with productive cough and treatment for those with sputum positive, is the policy of PAHO and the health ministries of Latin America.

BCG vaccination of uninfected persons can produce high resistance to tubercule bacilli, nonetheless, the protection conferred has varied greatly in field trials. Because some trials have shown high protection, BCG is still recommended in areas of high-transmission risk. The resolution of the question of BCG effectiveness needs further evidence.

Cancers

Cancers deserve mention in the context of this technical memorandum. They are already one of the leading causes of death in Latin America. This is an unhappy indicator of progress against other causes of mortality, because to die of most cancers, one must survive past middle age.

Epidemiologic research has identified varying patterns of site-specific prevalence in the region. This points out areas for research on risk factors as possible causes. Extremely high rates of cervical cancer and penile cancer, compared to the rest of the world, occur in several of the Latin American countries, including Panama.

RELEVANCE OF RESEARCH AT GORGAS

The relevance of GML research may be evaluated in comparison to the health problems of Panama, the tropical Americas, the United States, and to biomedical research in general. The broad range of pressing health problems in Latin America and the modest amounts of research support available dictate that careful stewardship and rational integration of resources and activities take place so that research programs do not overlap unproductively and that the restricted resources are used efficiently.

Historically, GML has concentrated on vector-borne parasitic and infectious diseases. Consequently, it is not surprising to note that GML has no active research program on malnutrition, leprosy, or tuberculosis. These health problems, however, are under active research and study by other institutions in the region. For example, malnutrition is the focus of a longstanding agenda of research and intervention studies by INCAP in Guatemala, by CFNI in Jamaica, and others. Leprosy research is carried out by CEPIALET in Venezuela, and the U.S. Public Health Service in Carville, La., while PAHO and philanthropic institutions also provide other support for research and intervention in several countries of the region. Tuberculosis research and training is also funded by PAHO. Thus, a lack of GML activities in these areas, by itself, does not indicate low relevance.

On diarrheal disease, GML has researched Campylobacter-caused diarrhea in Panama which was found to be very prevalent in hospitalized cases. Another recent study examined epidemiologic features of Norwalk virus and *Escherichia coli*. This work complements other diarrhea disease work in the region, such as rotavirus research by INCAP and the Caribbean Epidemiology Center.

A recent GML collaborative clinical study of oral rehydration therapy (95), published in the *New England Journal of Medicine* and also in Spanish in the *Revista Medica de Panama*, documented the wide applicability of this technique that was highlighted by an accompanying editorial (12). Thus, GML exploited the availablity of a health problem to expand basic scientific understanding, to test clinical therapy, and to disseminate the knowledge in Latin America and the United States.

Malaria research utilizes the GML monkey colony to test experimental drugs. The spread and multiplication of drug-resistant malaria is a cause for concern throughout the world emphasizing the need for discovery and testing of new therapeutic drugs. GML research has identified several promising compounds. This work is not only relevant to the countries with high-malaria prevalence, but also to the U.S. military, which in fact supports much of this research.

The *Aotus* monkey also appears to be a good animal model for leishmaniasis, which has been used at GML to test therapeutic treatment with allopurinol (119) of this disfiguring, sometimes fatal, disease. The GML monkey colony constitutes a resource to conduct screening of promising anti-leishmanial drugs.

Cancer is a growing concern in Panama, as well as the rest of Latin America, to which GML has responded by assisting in the development of a cancer registry utilizing the computer facility at GML. One result is the identification of a focus of strikingly high prevalence of cervical and penile cancers. Continuing research has since examined various epidemiological parameters, and has also shown a very high prevalence of a cancer-associated virus (HTLV) in this population. This is being investigated under a grant from the National Institutes of Health (NIH) and the National Cancer Institute (NCI). This work appears to be highly relevant to the region and especially to Panama. This finding was corroborated by the Minister of Health of Panama (34).

Epidemiological capability at GML is available to assist in epidemic outbreaks, such as occurred in 1981, with aseptic viral meningitis and with acute hemorrhagic conjunctivitis. GML's laboratory expertise for diagnosis of viruses complemented these investigations. GML maintains one of the few viral diagnostic capabilities in the tropical Americas. This type of activity is very important to Panama and the region.

Current research on Chagas' disease is surveying the human populations in two geographical areas of Panama in which different vector species transmit the *T. cruzi* parasite to determine epidemiological differences in the transmission cycles. This is under a grant from WHO.

Arbovirus research, especially on the vectors and reservoirs, is a major GML activity. A large effort is expended to monitor jungle yellow fever, using a system developed by GML, in the belief that surveillance can give early warning of epidemic potential. Urban yellow fever has not occurred for several decades in Latin America, but the vector *Aedes aegypti* is abundant throughout the region, including the United States. When an epizootic of jungle yellow fever flares, there is a probability of spillover transmission to humans, but, worst of all, would be involvement of *A. aegypti* in the transmission. Furthermore, there still remain questions about reservoirs and vectors of this disease. For Panama and Latin America, the relevance is obvious. For the United States, too, the relevance is not just theoretical or abstract. There are 20,000 U.S. Government employees and dependents in Panama, another 20,000 U.S. citizens in neighboring Costa Rica (51).

St. Louis encephalitis is another focus of arboviral research. GML is attempting to elucidate how the virus is maintained in tropical areas, the vectors and reservoirs, in order to expand knowledge of this arboviral disease that is prevalent throughout Latin America and the United States.

Research on insect vectors and animal reservoirs of other diseases is carried out as well at GML. Two important functions of entomologic field studies are discrimination of vector and nonvector species in various localities of actual and potential transmission (different species have varying transmission capabilities in different habitats), and elucidation of vector behavior and bionomics (e.g., biting times, resting habits, insecticide susceptibilities) in order to develop intervention strategies and to understand the interaction of host, parasite, and vector. Work at GML has recently demonstrated that a common blackfly of Panama, *Simulium quadrivittatum,* can function as a vector of onchocerciasis, though the disease is currently unknown there. Endemic foci of this disease occur in neighboring countries, thus the disease could spread. Recent work at GML demonstrated that transovarial transmission of yellow fever occurs in one of the mosquito vectors. Thus, the vector may also function as a reservoir of the virus, that may explain the persistence of the virus in the absence of disease in animal hosts. Identification of reservoir hosts is an important adjunct activity. Reduction of disease is sometimes feasible through control of animal hosts (e.g., China claims to have reduced leishmaniasis through control of dogs that harbor the parasite.) These activities have relevance to possible intervention in

Panama and the region, as well as to basic understanding of disease processes.

GML maintains a reference capability (available to the region as a WHO Collaborative Research Center) for the identification of blood meals in suspected insect vectors. This is used to determine host-preference from field-collected specimens throughout the region.

Investigation by isozyme electrophoresis* of disease vectors is carried out by GML. Identification of these biochemical markers improves the differentiation of vectorial status, especially where species complexes are involved. GML is examining sandfly vectors of leishmaniasis. Isozyme identification was also developed to differentiate the *Leishmania* species isolated from cutaneous sores. This can diagnose the mucocutaneous type before the destructive pathology develops.

Recently, ecological studies on the effects of impoundment of the Bayano River on insect populations and arbovirus activity have been carried out on contract. Also, environmental and disease impact assessments were carried out in connection with the Tabasara Hydroelectric Project. Relevance seems obvious given that the work was carried out under contract with a third party (the Government of Panama), but the relevance is several-fold:

1. the scientific merit and addition to scientific knowledge;
2. that environmental concern is being addressed and promoted in a developing country;
3. related to the development of environmental concern in Panama is the significant role that environmental preservation plays in the continued function and maintenance of the Panama Canal, a gravity-flow, natural watershed-fed navigational waterway; and
4. that GML was contracted, recognizing it as a body of expertise, within Panama, competent to do the work.

GML's work in sexually transmitted diseases (STDs) has focused on forms of STD that are of high prevalence in Panama, as well as surrounding countries of the region. STDs are epidemic in tropical America, as they are in the rest of the world, but very little public health activity is currently underway in Latin America or the Caribbean:

> With the exception of the four nations mentioned above [Canada, United States, Costa Rica, Cuba], few countries have been able to carry out well-organized STD control efforts. Although most countries have developed guidelines and standards for diagnosis and treatment, few programs to carry them out exist, especially outside large cities (76).

GML research on STDs in tropical America is an early and unique effort. For a problem of large magnitude with very little current information or other research underway, relevance to the needs of Panama and the region seems to be very high.

GML physicians see about 1,000 patients each year. These are people suffering from a variety of tropical diseases for which GML can provide expert and specialized services lacking among local physicians and clinics. This clinical service not only adds to the research effort at GML but also supplies a superb and unique teaching facility, and evidently creates much good will among the general, and health professional, population in Panama.

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*Isozyme electrophoresis is a method of separating and identifying variant proteins in apparently similar organisms which then permits differentiation and classification. This is most useful when it correlates with geographic, pathogenic, or other varying characteristics of the organisms.

SUMMARY

Overall, the work of GML appears to have high relevance to tropical Latin America, especially to Panama, to tropical disease research in general, and to the United States' interests. Not every activity of GML has obvious relevance.* Nonetheless, the Office of Technology Assessment finds that there is no major problem relating to the relevance of GML's areas of research. This finding is supported by the information presented above, by the personal statements of officials of Panama's Ministry of Health and other health professionals in Panama, by award of grant and contract funding of research projects by NIH, the Department of Defense, WHO, and the Government of Panama, by Fogarty International Center (FIC) site visit reports, and by NIH/FIC testimony before congressional committee.*

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*Clearly stated objectives and goals for the institution, as well as individual projects, together with regular, at least annual, formalized intramural review procedures could improve this situation.

*House of Representatives, Committee on Appropriations, 98th Congress: Subcommittee on the Departments of Labor, Health and Human Services, Education, and Related Agencies, Appropriations for 1984, National Institutes of Health, Part 4B, April 1983, pp. 1635-37, 1641-43.

Chapter 5

Findings and Conclusions

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FINDINGS

Previous chapters have presented information on the quality and relevance of tropical medicine research at the Gorgas Memorial Laboratory (GML). At the same time, they were designed to provide enough information about tropical diseases, tropical disease research, and research criteria so that research policymakers could place GML's quality and relevance in the context of the goals and capabilities of any comparable organization.

Gorgas cannot be compared to the National Institutes of Health (NIH). Neither can Panama's medical research system be compared to that of the United States. The differences depend on more than simply size. For example, the disease patterns differ, the level and organization of health care delivery differ, and availability of equipment and collaborating scientists differ. Field conditions both create obstacles and present opportunities that cannot be duplicated by an organization such as NIH.

OTA thus finds that **the evaluation of the quality of an institution such as Gorgas cannot take place without explicit recognition of certain premises.** The following are the premises assumed by OTA during this evaluation:

- There is an inherent value in supporting tropical research laboratories in tropical countries. These benefits (see the last section of ch. 1) extend to the tropical country, tropical regions in general, and to the country supporting the activities.
- Evaluations of the *quality* of research are inevitably, and properly, made partly on the basis of fairly objective criteria such as publications record and partly on the basis of subjective judgments by qualified individuals.
- The criteria used to judge quality, although similar in type, need to be modified and weighted differently for basic research or research performed in well-equipped, state-of-the-art laboratories than for field research laboratories.
- Relevance is directly dependent on the type and location of institution, and it should be examined from each of the appropriate viewpoints (e.g., host country, region, United States, general advancement of knowledge).

With these premises in mind, OTA examined the quality of GML's research against a range of objective and subjective criteria. There was very impressive agreement among the results of: 1) the past scientific evaluations of GML, 2) the critical evaluation of the research design and presentation of articles and manuscripts, 3) the survey of expert scientific opinion on GML's quality, 4) interviews with Panamanian health officials and professionals, 5) the examination of the GML staff's publications record, and 6) an examination of GML's record of competing for grants and contracts. All evidence gathered by OTA led to the finding that **the overall scientific quality of GML is high, especially when considered in the context of its status as a research laboratory located in the Tropics.** Quality was, naturally, not uniformly even, but it also appears that the Gorgas Memorial Institute's and GML's management is aware of unevenness and is attempting to make improvements.

Relevance is more difficult to judge, but in general OTA found that the large majority of GML's research is highly or adequately relevant to health concerns and problems of Panama, the tropical American region, U.S. interests, and the advancement of scientific knowledge and the field of tropical medicine in general (see tables 1 and 2 in ch. 1). The evidence for this finding lies, for the first two, in the match up between tropical health problems and GML research directed at them, and from strongly expressed opinions and examples by the Panamanian Minister of Health (who is a former Dean of the Panamanian School of Medicine), his Deputy Minister, the medical director of Panama's Childrens' Hospital (a former Minister of Health and former head of Social Security in Panama), and numerous officials of the Pan American Health Organization.

The importance of GML to Panama cannot be judged solely on the basis of Panama's monetary contribution. Panama is going through a difficult economic period. Even so, the Ministry of Health has arranged a loan to keep GML in operation for the remainder of fiscal year 1983. The value of the land, buildings, and tax-favored status have never been adequately assessed. And to put the often criticized direct financial contribution of $10,000 from Panama in perspective, the research budget of the Panamanian medical school is reportedly only $20,000 (34).

As one official of the U.S. Department of State expresses it: Each year, the United States sends a message to Panama and the region by funding GML and supporting activities related to the health of U.S. and Panamanian citizens alike (51).

Activities related to the recent Panama Canal treaty process provide a specific example of the importance of GML to Panama. As part of the treaty, a Joint Committee on the Environment was established. Panama turned to GML, as the only institution in Panama with the necessary skills and experience, for assistance in relation to environmental protection and human and animal health, and additionally named Dr. Pedro Galindo, formerly of GML, as the senior Panamanian on the Committee.

Relevance to U.S. health interests can be found in the surveillance activities, the training activities, and the various research activities undertaken under contract to the U.S. military. Gorgas' contributions in the areas of malaria, yellow fever, and leishmaniasis illustrate its relevance to the general advancement of knowledge.

Based on the above evidence, OTA finds that **with some exceptions that occur almost entirely within the core-funded activities, the research conducted at GML is relevant to the various parties at interest.**

CONCLUSIONS

OTA concludes that the benefits of supporting GML justify, on scientific and other grounds, the relatively small amount of funds required. Quality and relevance are high. Withdrawing core support from GML would probably not even save the amount of the appropriation, since other Federal agencies, such as the Department of Defense, may need to either develop their own capabilities to conduct research now carried out at GML or to fund similar research at other tropical medicine research centers.

Gorgas is not ideal; improvements could certainly be made. Some of the shortcomings stem from its uncertain funding. As mentioned earlier, the prospect of unstable funding and perhaps closure may have kept individual scientists from joining GML or becoming visiting scientists there and may reduce the desire of U.S. universities to collaborate with GML on research projects. As an example, two highly qualified entomologists from the United States discussed with GML the possibility of their coming to GML for a period. Uncertainties over the budget and the very future of GML have resulted in not being able to join GML, although one is still considering doing so.

The point about uncertainty should be placed in perspective: most research scientists operate under some degree of uncertainty about future funding. In GML's case, the uncertainty applies to the very existence of the entire institution. Thus, the uncertainty is a matter of degree (though perhaps a significant one), and not a situation unique to GML.

Another example of the effect of uncertain funding has been the decision by the U.S. Navy to hold off on the next scheduled training class, because the course would extend a few weeks into fiscal year 1984.

Gorgas itself could improve its standing and its relevance by:

- being more aggressive in its publishing;
- by making better use of its Advisory Scientific Board (e.g., in planning for research di-

rections, as part of a more formal and effective peer review process and as visiting consultants);

- by more actively seeking out associations with universities and collaborations with a range of groups from other countries and international organizations;
- by making strategic plans to move more fully into the developing areas of modern science (e.g., work with monoclonal antibodies and other immunological diagnostics, and biotechnology approaches to vaccine-related research and development*);
- by making more of an effort to run vigorous visiting scientist and fellowship programs; and
- similar types of actions that should be considered by GMI/GML at a very near date.

Gorgas has also done a rather poor job of letting Congress, Panama, and the public know how much it is doing and what its capabilities are. Its financial base should be broadened. Alternately, or in combination with broadening, some change in the structure (e.g., an international arrangement of support) of GMI/GML might be undertaken. Any such step should be taken carefully, in view of the importance of GML and its activities (e.g., its disease surveillance work) to the United States.

OTA concludes that the only benefit to the United States of defunding Gorgas would be saving of perhaps significantly less than $2 million. The negative consequences would include loss of one of the few, high-quality, broadly relevant, tropical research institutions located in a tropical country. The Army's malaria research would be hurt, as would disease surveillance in the Central American region. The U.S.'s standing in Panama, and perhaps more broadly in tropical America, would inevitably suffer. For example, the lead editorial on July 7, 1983, in Panama City's leading newspaper spoke emotionally of the "incomprehensible budget policies" of the United States in regard to defunding Gorgas.

Ironically, GML is in danger of extinction at the very time that U.S. interest in Latin America is high, and at a time when tropical medicine has never been more relevant to the United States. Health aspects of the increased numbers of refugees in the United States, an increased amount of international travel, and the growth of multinational corporations located in tropical regions are examples of this heightened relevance.

Loss of the training activities at Gorgas would not only hurt the U.S. Navy but would also preclude the desirable possibility of expanding such training in tropical medicine to include more visiting physicians and students in health sciences* from the United States and to increase the number of Panamanians and others attending.

In summary, OTA concludes that the positive consequences of U.S. core support of Gorgas greatly outweigh the amount of funds involved. Defunding now, followed by an appreciation of the loss later and a subsequent attempt to reinstate such a research capability, may result in much larger required investments, an inability to recreate successful conditions for quality research, or both.

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*The contributions of the International Laboratory of Research on Animal Diseases in Kenya to the molecular biology of African trypanosomes is an example where a field unit has done important work at the forefront of science (68). Other good examples are the centers supported by the Rockefeller Foundation's Great Neglected Diseases Program.

*For example, GML and Yale University have an ongoing program whereby students of Yale's School of Medicine go to GML for 2- to 3-month periods for experience in research and clinical aspects of tropical medicine.

Appendixes

Appendix A

Acknowledgments; Pan American Health Organization Liaison Group; OTA Health Program Advisory Committee

ACKNOWLEDGMENTS

The development of this technical memorandum was greatly aided by the advice and review of a number of people in addition to the Pan American Health Organization Liaison Group, and the Health Program Advisory Committee. OTA staff would like to express their appreciation especially to the following individuals:

Thomas Aitken
Yale University
Maj. Richard G. Allen
United States Army Medical
Research Command
Karen Bell
National Academy of Sciences
Mark S. Beaubien
Fogarty International Center
Mark Boyer
Harvard University
Louise Brinton
National Cancer Institute
Gloriella Calvo
The Gorgas Memorial Institute
Cdr. Patrick Carney
Navy Research &
Development Command
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Harvard University
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Tulane University School of Medicine
William Collins
Centers for Disease Control
Joseph A. Cook
The Edna McConnell Clark Foundation
Gustave Dammin
Harvard University
William Dietz
Clinical Research Center
Col. Carter Diggs
Walter Reed Army
Institute of Research
Jose Renan Esquivel
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Panama City
Phyllis Eveleth
Fogarty International Center
Allan Fleener
General Accounting Office
Gaspar Garcia de Paredes
Minister of Health
Republic of Panama
Robert J. A. Goodland
The World Bank
Col. Michael Groves
Walter Reed Army
Institute of Research
Sherman Hinson
U.S. Department of State
Rod Hoff
Harvard University
Donald Hopkins
Centers for Disease Control
Abraham Horowitz
Pan American Health Organization
Lee Howard
Pan American Health Organization
Leon Jacobs
The Gorgas Memorial Institute
Geoffrey Jeffries
Centers for Disease Control
Karl M. Johnson
Fort Detrick
William Jordan
National Institute of Allergy
and Infectious Diseases
Irving Kagan
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Robert Kaiser
Centers for Disease Control
Cpt. James F. Kelly
Commanding Officer
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Dieter Koch-Weser
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Youngstown State University
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Agency for International Development
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Col. C. J. Peters
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Gorgas Memorial Laboratory
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The World Health Organization
Special Programme for Research and
Training in Tropical Diseases
Ira Rubinoff
Smithsonian Tropical
Research Institute
Col. Phillip K. Russell
Director
Walter Reed Army Institute
of Research

- Rolando E. Saenz
  - Gorgas Memorial Laboratory
- Warren R. Sanborn
  - Portable Rapid Diagnostic Technology, Inc.
- John E. Scanlon
  - American Society of Tropical Medicine and Hygeine
- Robert E. Shope
  - Yale Arboviral Research Unit
- Reuel A. Stallones
  - University of Texas
- Ronald St. John
  - Pan American Health Organization
- Jose Teruel
  - Pan American Health Organization
- Paul Tiggert
  - Gorgas Memorial Institute
- Ronald Vogel
  - University of Arizona
- Kenneth Warren
  - The Rockefeller Foundation
- Raymond H. Watten
  - Director
  - Gorgas Memorial Laboratory
- Thomas Weller
  - Harvard University
- Karl A. Western
  - National Institute of Allergy and Infectious Diseases
- Kerr L. White
  - The Rockefeller Foundation
- Roy Widdus
  - National Academy of Sciences
- Frank S. Wignall
  - United States Navy
- Phillip Winter
  - Walter Reed Army Institute of Research
- Martin Wolfe
  - U.S. Department of State
- Martin Young
  - University of Florida

PAN AMERICAN HEALTH ORGANIZATION LIAISON GROUP

OTA would like to thank the members of the group formed by the Pan American Health Organization to provide advice on OTA's study of the Gorgas Memorial Laboratory and the main project on the status of research for tropical medicine in tropical America.

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Appendix B

Tropical Disease Research Activities

This appendix is a brief profile of tropical medicine research support, concentrating primarily on activities with which the United States is involved, either through direct research activities or by block contributions, but also containing several examples of other supporting organizations. Table B-1, at the end of this appendix, summarizes the tropical medicine research funding levels of the organizations covered. This discussion should not be regarded as a comprehensive review. For example, many U.S. universities maintain tropical biomedical research programs. In addition, most developed and some developing countries have national agencies or institutes which in some way fund tropical disease research. These are not covered. For more detail on the range of support for tropical medicine research, see the General Accounting Office report on Gorgas, to be completed in August 1983.

Multinational Programs

The **United Nations Development Program/World Bank/World Health Organization** Special Programme for Research and Training in Tropical Disease (TDR) has targetted six specific diseases for biomedical research: malaria, schistosomiasis, filariasis, African and American trypanosomiasis, leishmaniasis, and leprosy. Essentially a grant institution, TDR also funds projects on vector biology and control, biomedical sciences, epidemiology, and social and economic research (126). Of the more than $30 million spent by TDR in 1981, appproximately $5.6 million went to research activities in the Americas (77). Total U.S contributions to the TDR in 1982 were more than $5 million, approximately 22 percent of all TDR fundings (105).

The **Pan American Health Organization** (PAHO), regional office of the World Health Organization, sponsored 131 research projects during 1980-81 for a total of $5.2 million. Direct monetary contributions from PAHO/WHO comprised 32 percent of that sum, the remainder coming from the 30 institutions, international organizations, agencies, and governments that collaborate with PAHO. Research efforts were primarily directed towards the diarrheal diseases, a reflection of the Special Programme for the Control of Diarrheal Disease. PAHO-funded programs also researched other infectious diseases, parasitic diseases, foot and mouth diseases and vesicular stomatitis, zoonoses, nutrition, and other areas (77). In 1982-83, U.S. contributions to PAHO of $57.1 million constituted 61.3 percent of the organization's funding (18).

PAHO maintains nine centers, including the Caribbean Epidemiology Center (CAREC) located in Port-of-Spain, Trinidad, the Institute of Nutrition of Central America and Panama (INCAP) in Guatemala City, the Caribbean Food and Nutrition Institute in Kingston, Jamaica, and the Pan American Center for Research and Training in Leprosy and Tropical Diseases, in Caracas, Venezuela (76). PAHO provides scientists and researchers to each of the centers, and with the exceptions of INCAP, which is semi-independent, and CAREC, which receives moneys from 19 different countries and institutions, the centers are primarily PAHO- funded. It is important to note that the centers are by no means exclusively devoted to research. CAREC, for example, provides extensive training, epidemiological surveillance, and laboratory services for much of the English-speaking Caribbean (100).

United States Agencies

The majority of **Agency for International Development** (AID) funding for tropical diseases research comes from its Office of Health. In fiscal year 1982 the office allotted $5.8 million for research in malaria immunology and vaccine development, $5 million to the TDR, and $1.9 million as part of the core support for the International Center for Diarrheal Diseases Research/Bangladesh. The AID Africa Bureau spent approximately $1.3 million on the biomedical research components of three projects—onchocerciasis control, combatting communicable childhood diseases, and schistosomiasis activities in the Cameroons and the Sudan. The remainder of AID's tropical diseases activities, some $1 million, was channeled through the Office of the Science Advisor for collaborative research between U.S. universities and developing countries. All AID funding may be considered "extramural," with moneys given out on a competitive basis to universities, profit, and nonprofit institutions (79).

Nearly all tropical diseases research at the **National Institutes of Health** (NIH) is carried out at the **National Institute of Allergy and Infectious Diseases** (NIAID). NIAID spent more than $9.5 million in fiscal year 1982 for research on trypanosomiasis, schistosomiasis, leishmaniasis, malaria, filariasis, and leprosy. The General Tropical Medicine Program spent $7.7 million for research involving virology, bacteriology, vector pathogens, and other disciplines; NIAID's General Parasitology Program expended an additional $3.5 million. The NIAID International Collaboration in Infectious

Diseases Research (ICIDR) Program allies institutions in tropical countries with universities in the United States for joint research on specific diseases. The ICIDR fiscal year 1982 budget was $2.2 million. Another $800,000 was directed towards NIAID Tropical Research Units (112). Approximately $9.5 million of the NIAID's Tropical Medicine Program expenditures went towards intramural research, including salaries and administrative costs. Extramural research accounted for the remaining $25 million, awarded to institutions around the world on a competitive grant basis. The NIAID Tropical Medicine and fiscal year 1982 total came to $34.8 million.

Also within NIH, the **Fogarty International Center** administers the appropriation of the Gorgas Memorial Institute (as the core support for the Gorgas Memorial Laboratory).

The **Department of Defense** (DOD) is active in areas of research into diseases which pose a threat to American troops stationed in tropical regions. Activities within DOD are coordinated by the Medical Research and Development Commands of the Army and Navy. Within the Army, tropical disease research is managed by the Research Area Manager for Military Disease Hazards; the Infectious Diseases Program Manager oversees the Navy's activities. In fiscal year 1983, DOD expenditures are estimated at $31.2 million, more than half of which ($17.6 million) was directed towards "basic" research (2).

The Walter Reed Army Institute of Research is the center for most of the Army's tropical disease activities. In the Navy, the Naval Medical Research Institute is the major U.S.-based center for tropical diseases research. Infectious diseases research includes a wide range of tropical diseases. The Army's antimalaria drug development program and the Navy's vaccine effort are part of the Department's emphasis on malaria. In addition, the United States Army maintains tropical medicine research units in Brasilia, Kenya, Malaysia, and Thailand. The Naval Medical Research Units are located in Manila, Jakarta, Lima, and Cairo. In fiscal year 1983 DOD funding for these overseas units came to $9.7 million. The department's overall tropical disease program total of $31.2 million does not include salary or housing expenses for military personnel, which fall into other areas of DOD obligations; however civilian salaries, local employees, maintenance, and supplies do come out of tropical disease program budgets.

The **Centers for Disease Control** (CDC) (of the U.S. Public Health Service) does not have an autonomous tropical disease program, but conducts tropical disease research primarily through its Center for Infectious Diseases and its Parasitology Division. CDC also serves as a worldwide resource center and is frequently called on by tropical countries to provide emergency assistance. The Medical Entomology Research and Training Unit in Guatemala is funded by CDC. In fiscal year 1983, total CDC tropical diseases research funding, including salaries, administration, and other costs, came to an estimated $5.5 million (53).

Other Institutions

The following are a few examples of non-U.S. Government supporters of tropical medicine research and related activities.

Through its Tropical Diseases Research Program, the **Edna McConnell Clark Foundation** funds a variety of research projects in both developed and developing countries. Primarily concerned with schistosomiasis, the foundation's program awarded approximately $2.5 million for more than 60 competitive grants during fiscal year 1982, and accounted for 18 percent of all Clark Foundation activity (27).

The Great Neglected Diseases of Mankind (GNO), a major component of the **Rockefeller Foundation** Health Sciences Program, examines vaccine and drug development, improvement of diagnostic testing, and appropriate targeting of therapy. The GND Network currently maintains 14 units at institutions around the world. These units, primarily universities, carry out research projects concentrating on malaria, schistosomiasis, and diarrheal diseases; furthermore, in 1982 the units trained a total of 84 researchers from developed and developing countries. The GND program cost came to $1.9 million in 1982 (90).

The **International Development Research Centre** (IDRC), an Ottawa-based public corporation created by the Canadian Parliament, disbursed approximately $4.9 million Canadian on tropical medical research grants to institutions in 1982 from its Health Sciences Division. The grants went for projects ranging from sexually transmitted diseases to malnutririon to leprosy. The division also provided additional funding for some health care delivery and water supply and sanitation projects in tropical countries. Along with its four other divisions, IDRC issued $36.5 million in grants during 1982 (56).

In London, a portion of the profits profits from the Burroughs-Wellcome pharmaceutical company go to the **Wellcome Trust**. During 1980-82, the Trust distributed 3.6 million pounds Sterling (roughly $6 million U.S., approximately 15 percent of the Trust's total allocations) for research and fellowships for investigation into cerebral malaria, schistosomiasis, leishmaniasis, rabies, and other tropical medicine concerns. About 30 percent of these funds were used to help run the Trust's Tropical Units in India, Brazil, Thailand, Kenya, and Jamaica. Approximately 20 percent of the allocations were used for special lectures and fellowships with the remaining 50 percent awarded to researchers and research institutions around the world on an individual project basis (122). In addition, the **Burroughs Wellcome Fund**, an entirely separate entity supported by profits from the U.S. branch of the company, awarded $406,000 in support of molecular parasitology research in fiscal year 1982. This sum represented 18 percent of the Fund's awarded grants during that period (80).

Table B-1.—A Profile of Funding for Tropical Medical Research

Organization	Millions of dollars	Year	Reference
World Health Organization:			
Special Programme for Research and Training in Tropical Diseases (TDR)	23.832	81	102
Pan American Health Organization	5.2	80-81	77
Agency for International Development	15.0	FY82	79
National Institutes of Health:			
NIAID	34.856	FY82	111, 112
Fogarty International Center	1.8	FY83	114
Department of Defense	31.246	FY83	2
Centers for Disease Control	5.5	FY83	53
Edna McConnell Clark Foundation	2.573	82	27
Great Neglected Diseases Program	1.9	82	89
International Development Research Centre	4.2[a]	82	56
Burroughs-Wellcome	6.6[b]	80-82	80, 122

[a] Approximately equal to 4.9 million Canadian dollars.

[b] Approximately equal to $600,000 U.S plus 3.6 million pounds Sterling.

NOTE: The definitions of tropical diseases and tropical disease research activity used in compiling these data are not uniform. For example, CDC totals include activity in research which is not covered by the Department of Defense. TDR/WHO totals are for research and development and research capability strengthening only. The DOD data are only restricted to those diseases which are of concern to American troops stationed in tropical countries. As part of the Department of State, AID contributes funds for tropical disease research to both the TDR/WHO and the PAHO; these funds then lose their "American" label. In addition, more than $1 million was given by AID to NIAID. Only 32 percent of PAHO activities came directly from PAHO/WHO, the remainder coming from matching contributions from local governments.

Appendix C

Bibliography of Publications by the Gorgas Memorial Laboratory Staff

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LISTA DE LAS PUBLICACIONES DEL LABORATORIO CONMEMORATIVO GORGAS DE 1975 A 1979[+]

(EN LOS 50 AÑOS DE SU FUNDACION)
CON ADICIONES PARA 1980

Prof. Manuel Víctor De Las Casas[++]

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[++] Bibliotecólogo Médico del Laboratorio Conmemorativo Gorgas y Profesor de Bibliotecología en la Facultad de Filosofía, Letras y Educación, de la Universidad de Panamá.

[*] El asterisco que sigue al número de una publicación indica que, al momento de preparar esta bibliografía, hay disponibles reimpresos de la misma.

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ADDENDA – 1980

Conmemorando 50 años de la aparición de nuestra primera publicación.

(Los números son asignados a las publicaciones en el mismo órden en que éstas van llegando a la Biblioteca del Laboratorio Conmemorativo Gorgas)

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Appendix D

Summary of the Telephone Survey on Gorgas Memorial Laboratory

Conducted July 13-17, 1983

Michael B. Macdonald, under contract to OTA, conducted a telephone survey of experts knowledgeable about the Gorgas Memorial Laboratory (GML). OTA supplied Mr. Macdonald with a list of approximately 70 potential interviewees. He attempted to contact each of them, and was able to complete 23 interviews. (The individuals contacted are among those included in the Acknowledgments for this memorandum.)

The original list of potential interviewees was compiled by OTA staff. It included the names of individuals known to have specific knowledge of GMI/GML. The names were gathered during the previous 2 months of preliminary work on this technical memorandum. During that process, solicitations were continually made for additional people who would have useful information on this subject. Names were added to the list regardless of whether biases of the individuals were known or unknown to OTA, and regardless of the nature of those biases. The wide range of responses, positive and negative, gives some assurance that a spectrum of viewpoints was expressed, though OTA does not claim the survey to be global or entirely representative of opinion about Gorgas.

Most of those contacted by Mr. Macdonald had some firsthand knowledge of Gorgas. They had either worked there, collaborated with Gorgas investigators, participated in site visits, or had experience with Gorgas grants or contracts. Nearly all those who participated in the survey are technical specialists in tropical diseases, including experts in infectious diseases (mainly arboviruses and other viruses); malaria, leishmaniasis, helminthic, and other parasitic diseases; traditional tropical disease and cancer epidemiology; vector biology; microbiology; nutrition; and the general fields of clinical research, tropical medicine, preventive medicine, and international health.

Ten of the participants hold positions in U.S. academic institutions, five are in the military, six are employed by other U.S. Government departments (Department of Health and Human Services and Department of State), and two are with an international health organization.

The results of the survey are summarized in the remainder of this appendix. Opinions and quotes are not attributed to specific individuals.

1. How would you rate the work of GML?

The respondents generally rated the quality of work at GML high. Most felt that some programs were excellent, especially the work on arboviruses, malaria, and medical entomology, while other programs, such as the bacteriology, were of lower quality. Three respondents said that GML has done excellent work. The most solid endorsement came from one who said that it was "outstanding, the best in the world." Two others who have spent many years in tropical medicine stressed that the location of GML makes it an excellent site for training, as a place for visiting scientific groups, and for field situations that are not available elsewhere.

Other responses were less enthusiastic but still generally positive. Some programs were considered excellent, others less so. One person commented, "Like any large institution which has existed for many years, it has its weak points, but on a scale of 1 to 5, I would give it a 4 (high)." Another offered a similar rating. He felt that while some of the research may not be original, it is technically very good.

Certain programs, including the entomology, virology, and malaria work got high marks. Other programs that were rated as excellent were the cancer and sexually transmitted diseases programs, trypanosomiasis and leishmaniasis studies, and the ecology and environmental studies.

One respondent said that while the arbovirus and ecology studies were excellent, some of the other programs were "mediocre." Another individual commented, "some of the work was excellent, some routine, but you can expect that in any institution that has existed for so many years."

The bacteriology and some parasitology programs were sometimes said to be the weakest points. Two respondents characterized some of the parasitology studies as slow but steady.

Many chose to qualify their answer and said that one must consider the setting when rating the work of GML. The field conditions make it a much different situation than that of the National Institutes of Health (NIH), for instance. One person commented, "I would rate the work as high. As a person who has worked in the field for many years, I know what tropical medicine work is like. Its only weak point is the decrease in support which makes it difficult to attract top scientists." Another also rated the work as "undersupported."

2. How should GML be judged?

The quality of publications and GML's impact on the public health of the region were the most frequently offered criteria for evaluation. Other responses included judging how GML fared in grant competition; on the productivity of researchers; on the reputation of the staff; on the training provided at GML; and by the contributions to progress against specific diseases.

Those respondents with the most experience in the field stressed that one should not make a direct comparison between an institution such as GML and university or NIH laboratories. Some felt that it should be judged on a regional basis, in comparison to laboratories in other countries in the region. One individual pointed out that because many of the programs are involved in vector control, it is inappropriate to look simply at short-term output. The benefits of surveillance accrue in the long term.

3. Has the quality of research changed over the years?

Most of the participants agreed that this was a difficult question, since the emphasis of the research has changed. Many chose not to answer. Three thought that there was no change. Two said there had been a positive change. Four others said that there were fluctuations in the quality of research, but through all of the fluctuations, some programs, such as entomology, continued to meet a very high standard.

A number of people responded that there has been a general decline in the quality of the research over the years. All of those who said that there has been a decline blamed the uncertain funding, citing an inability to buy sophisticated equipment or attract top-notch scientists.

4. Are you aware of the Peer Review Process at GML?

Few had any knowledge of the peer review process at GML. There was a general lack of consensus about whether such a process exists. It seems that respondents felt that sometimes the peer review process was operating, while at other times it was not, possibly depending on who was in charge. One person commented that a process exists, but it needs strengthening.

5. What is the relevance of GML to research in: Panama, Latin America, the United States, and Biomedical Research in general?

In various ways, GML research is perceived to be relevant to Panama, the region, and the United States. A number of individuals noted that Panama benefits from activities such as the surveillance field studies and the environmental impact assessments of hydroprojects.

Another respondent, familiar with the cancer research, noted that GML has been a great help in increasing the sophistication of Panamanian cancer researchers.

In terms of the region, GML served as a serum and data bank during the recent dengue epidemic. It was also the only laboratory in the region that was capable of looking into the resurgence of yellow fever.

Another aspect of its importance as a regional center is that it is a place where researchers in Central and South America can call and receive answers in Spanish.

Everyone contacted mentioned that GML is particularly important to the United States, specifically for the military. Since NIH no longer has its own laboratory in Central America, it is the only place for the military to commission work in the region.

One respondent said that if GML did not exist, then the military would have to build its own tropical laboratory.

Many respondents stressed the *potential* impact of GML work. Some said it should be more closely linked to the Panamanian Ministry of Health, that it should be a leader in the region and that it could be more productive. One respondent, however, felt that political barriers presently limit its importance as a regional center.

6. What is the value of the training in tropical medicine carried out at GML?

Most of those who commented gave GML training a high rating. They felt that it was a unique setting and very important to maintain, since there are so few other places available for training in tropical medicine. One person said that a training center in a place such as Puerto Rico, for example, would not be as valuable because of a different disease ecology. Two respondents offered the same quote by General Douglas MacArthur that in the Philippines he needed three divisions to do the work of one, since two would always be in the hospital with malaria or dengue.

Not all of the responses to this question were positive. Two felt that the level of training had gone downhill over the past few years because of financial constraints. Another felt that the trainers were not sophisticated enough. He noted that there were more Panamanians involved in the training now and that the program was hurt when NIH cut back on funding for young American scientists to go to GML. A third negative opinion was offered by a university scientist who felt that there should be more civilians involved in training programs at GML.

7. What is the value to research of the animal population kept at GML?

Nearly all of the responses to this question were very positive about the animal populations. This question evoked the most immediate and strongest reactions of any on the survey. The colonies were variously termed "Crucial, Critical and Unique, cannot be duplicated elsewhere." One noted that this function is becoming even more important with the increasing prevalence of malaria strains resistant to current drugs. A number of respondents noted that it was much more cost effective to keep the colonies in Panama than in the United States. Besides malaria, the colonies are very important in the study of diseases such as trachoma and hepatitis.

One person stressed that the work on antimalarials *must* be carried out. He said that if GML cannot do it then the Army would have to build its own lab to screen the antimalarial drugs. Others concurred that this was one of the most important functions of GML. "The screening of antimalarials must continue." "The monkey colonies are invaluable to our study of human malaria." It was mentioned that to an outsider the colonies seem to be dull and routine work, but they provide a very important service.

One who is quite knowledgeable about malaria felt the value of the *Aotus* population had declined over the years and that there was some difficulty in meshing the colony to current research needs. He felt that the colony was not reaching its potential.

In addition to the monkey colony, it was menioned that the wild animals in the area also provide a very valuable resource for the study of disease ecology of such diseases as leishmaniasis, the arboviruses, and Chagas' disease

8. Do you have any suggestions for change?

Nearly all respondents had suggestions for change: stabilization of funding and increased funding were the most common answers.

It was felt that the constant budget problems eroded the confidence of the staff and GML's attraction to top scientists. One respondent who had worked there for many years said that it was demoralizing to hear at every weekly meeting that, "Funding might be cut next week." He said that uncertain funding was a major reason for failing to attract top university scientists. One said that GML cannot continue in such a precarious financial position and that it should either be funded properly or closed. Others felt that GML/GMI should look for more international support and operate more like the cholera research institution in Dacca or the International Laboratory of Research on Animal Diseases in Kenya.

Another respondent suggested that GML should collaborate more with labs in the United States, but bureaucratic changes would be needed for travel money and arrangements for cooperative agreements with other institutions.

Some felt that major changes should be made in the management structure of GML/GMI, expressing the opinion that even with solid core support, they would not be able to compete with other tropical medicine units. "The current direction must change" noted one individual. The need for a strong executive was recognized by many other respondents. One felt that they should pay the high salary needed to get a good director in the United States and in Panama. Two other scientists with many years of experience in tropical medicine felt also that it was important to develop closer ties to the region.

Other suggestions were for more long-range planning, a firmer peer review process and pruning the dead wood. Two felt that there should be closer links to basic science and a greater use of more sophisticated immunologic and diagnostic techniques.

9. What do you think is the overall value of GML?

All the respondents, without exception, felt that it would be a terrible mistake to lose GML. "For better or worse, it is the only one we have, and we are better off with something than nothing. If it did not exist [the military] would have to build one there." It is a resource that cannot be duplicated. "It is irreplaceable in the panorama of tropical disease research related to Latin America and the United States." A number of other respondents noted the unique setting of GML. "While it does have its weaknesses, it would be a terrible mistake to let it go." "The relative cost is peanuts compared to the benefits, and it would be insane to reduce our limited involvement in the area." "If lost now, we would never get it back."

Many spoke in terms of GML's potential. One felt that GML's value now was only marginal but that it could be great, if it had stable funding.

GML is also viewed as a front line defense against certain diseases that could spread to the United States. Panama Canal forms a barrier to many diseases at this point. But now that the Pan American Highway is opening up it is even more essential that diseases such as foot and mouth disease, swine fever, yellow fever, Venezuelan and eastern equine encephalitis be confined at this point.

Besides its importance in traditional tropical medicine, GML is very important in cancer research in the region. It is unique in that it is capable of doing sophisticated cancer research in a place which is in the process of modernization.

GML was also felt to be very important politically. It would be an affront to Panama if we pulled out as it is a very important indicator of U.S. concern with nonpolitical problems in the region. The general feeling was that with the current direction of events in the region, GML is becoming more important than ever, if constructive changes are made.

Appendix E

Glossary of Acronyms and Terms

Glossary of Acronyms

AFRIMS —Armed Forces Research Institute of Medical Sciences
AID —Agency for International Development (U.S. Department of State)
ARI —acute respiratory infections
BCG —bacille Calmette-Guerin Vaccination
CAREC —Caribbean Epidemiology Research Center (PAHO)
CCCD —Combatting Communicable Childhood Diseases (AID)
CDC —Centers for Disease Control (PHS)
CE/LAS —California Encephalitis/LaCrosse Encephalitis
CEPIALET —Pan-American Center for Research and Training in Leprosy and Tropical Diseases (PAHO)
CFNI —Caribbean Food and Nutrition Institute (PAHO)
DOD —U.S. Department of Defense
DRG —Division of Research Grants (NIH)
EEE —eastern equine encephalitis
EPI —Expanded Program on Immunization (WHO)
FIC —Fogarty International Center (NIH)
GAO —General Accounting Office (U.S. Congress)
GMI —Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc.
GML —Gorgas Memorial Laboratory (of GMI)
GND —Great Neglected Diseases of Mankind (Rockefeller Foundation)
HHS —U.S. Department of Health and Human Services
HTLV —human T-cell leukemia virus
ICDDRB —International Center for Diarrheal Disease Research/Bangladesh
ICIDR —International Collaboration in Infectious Diseases (NIAID)
IDRC —International Development Research Centre (Canadian)
ILRAD —International Laboratory of Research on Animal Diseases
INCAP —Institute of Nutrition of the Caribbean and Panama (PAHO)
IRG —Internal Review Group (NIH)
MARU —Middle American Research Unit (NIAID)
MERTU/G —Medical Entomology Research and Training Unit in Guatemala (CDC)
NAMRU —Naval Medical Research Unit
NCI —National Cancer Institute (NIH)
NIAID —National Institute of Allergy and Infectious Diseases (NIH)
NIH —National Institutes of Health (PHS)
ORT —oral rehydration therapy
OTA —Office of Technology Assessment (U.S. Congress)
PAHO —Pan American Health Organization
PHS —U.S. Public Health Service (HHS)
SLE —St. Louis encephalitis
STD —sexually transmitted diseases
TDR —United Nations Development Program/World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases
UNDP —United Nations Development Programme
USAMRU —United States Army Medical Research Unit
VEE —Venezuelan equine encephalitis
WEE —western equine encephalitis
WHO —World Health Organization
WRAIR —Walter Reed Army Institute of Research
YARU —Yale Arboviral Research Unit (Yale University)

Glossary of Terms*

acute: Having a sudden onset, sharp rise, and short course; not chronic.

Aedes (ah-ee'dez): A genus of mosquitoes. *A. aegypti*, the tiger mosquito, is a common urban species that breeds near houses and transmits urban yellow fever and dengue fever.

amebiasis (am-ee-bi'ah-sis): Infection by amebae, especially, infection with *Entamoeba histolytica*, an intestinal parasite, characterized by diarrhea with blood and mucous and also causing abcesses in the intestine and liver (sometimes called amebic dysentery). See AMEBA.

ameba (ah-me'bah), also, amoeba: A protozoan; a minute single-celled life form. One species, *Entamoeba histolytica*, is a parasitic pathogen producing amebiasis in man. See AMEBIASIS.

ancylostomiasis (an-ki'los-to-mi'ah-sis): Infection with *Ancylostoma duodenale*, the human intestinal hookworm. Causes chronic anemia.

Anopheles gambiae (a-nof'a-leez gam-bee'ee): A species of mosquito in Africa that transmits malaria; also, a group of closely related species of mosquitoes. See SPECIES COMPLEX.

antigen (an'ti-jen): Any substance that stimulates the production of antibodies.

Aotus (ay-o'tus): A genus of monkey; the owl monkey.

arbovirus (ar'bo-vi-rus): An abbreviation for arthropod-borne virus, virus transmitted by arthropods.

Argentinian hemorrhagic fever: An acute, sometimes fatal disease caused by a virus, transmitted through contamination by urine or feces of infected rats. Characterized by chills, fever, severe headache, hemorrhagic symptoms, shock, kidney involvement, and neurologic involvement.

arthropods (ar'thro-podz): Invertebrate animals of the phylum Arthropoda that includes insects, ticks, spiders, and crustaceans.

arthropod-borne: Transmitted by arthropods.

ascariasis (as-kah-ri'ah-sis): An infection with worms of the genus Ascaris, especially, *Ascaris lumbricoides*, the human intestinal round worm, characterized by intestinal pain and diarrhea.

aseptic meningitis (a-sep'tik men-in-ji'tis): Viral-caused inflammation of the membranes surrounding the brain and spinal cord.

bacille Calmette-Guerin, abbr. BCG: An attenuated (weakened) strain of tuberculosis bacteria used to vaccinate against virulent tuberculosis.

bacillus (ba-sil'us), pl. bacilli: Any of various rod-shaped, aerobic bacteria of the genus Bacillus.

bacteriology (bak-tir'ee-ol'o-ji): The scientific study of bacteria.

bacterium (bak-tir'ee-um), pl. bacteria: Any of numerous unicellular micro-organisms (class *Schizomycetes*), occurring in a wide variety of forms, existing either as free-living organisms or as parasites, and having a wide range of biochemical, often pathogenic, properties.

bilharzia (bil-har'zi-ah): See SCHISTOSOMIASIS.

bilirubin (bi-li-roo'bin): A pigment largely derived from the breakdown in the spleen of hemoglobin from red blood cells.

Bolivian hemorrhagic fever: An acute, sometimes fatal disease caused by a virus, transmitted through contamination by urine or feces of infected rats, occurring in Bolivia. Characterized by chills, fever, severe headache, hemorrhagic symptoms, shock, kidney involvement, and neurologic involvement.

California encephalitis: An acute encephalitis caused by an arbovirus, transmitted by mosquitoes.

Campylobacter (kam'pil-o-bak'ter): A genus of bacteria, one of which, *C. jejuni*, causes an acute diarrheal disease.

cellulose acetate electrophoresis: A type of isozyme electrophoresis. See ISOZYME; ISOZYME ELECTROPHORESIS.

cervical cancer (ser'vi-kal): Cancer of the cervix (the neck of the uterus).

Chagas' disease (sha'gus): Infection by *Trypanosoma cruzi*, transmitted by reduviid bugs. Discovered and described by Carlos Chagas of Brazil. Characterized by an acute course in children with fever, encephalitis, and inflammation of the heart muscle (often life-threatening or fatal), and a chronic course in adults leading to heart disease and heart failure. Widely distributed in Central and South America. Also called American trypanosomiasis. See TRYPANOSOMIASIS.

Chagres fever: A febrile disease caused by an arbovirus, transmitted by phlebotomine sandflies. Also called "Panama fever."

chemotherapy (kee-mo-ther'a-pi): The use of specific chemical agents to arrest the progress of, or eradicate, disease in the body without causing irreversible injury to healthy tissues.

chorioretinitis (kawr-i-o-ret-in-it'is): Inflammation of the choroid and retina of the eye.

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chronic: Lingering, lasting, as opposed to acute.

Colorado tick fever: A febrile disease without rash caused by an arbovirus, transmitted by a tick, occurring in the Rocky Mountain region of the United States.

cytogenetics (si'to-je-net'iks): Laboratory examination, usually microscopic, of chromosomes.

dengue fever (deng'gee): An acute febrile disease caused by an arbovirus, transmitted by mosquitoes of the genus Aedes, characterized by fever, severe pains in the head, eyes, muscles, and joints, and a skin eruption. Occurring in Japan, Southeast Asia, the South Pacific, India, the Caribbean, Middle and South America. Sometimes called "breakbone fever."

dengue hemorrhagic fever: Life-threatening complications of dengue infection; syn. DENGUE SHOCK SYNDROME. See DENGUE FEVER.

dengue shock syndrome: Life-threatening complications of dengue infection; syn. DENGUE HEMORRHAGIC FEVER. See DENGUE FEVER.

diarrhea (dy-a-ree'a): Pathologically excessive frequency and fluidity of fecal discharges. Adj., diarrheal.

diphtheria (dif-theer'ee-a): An acute infectious disease caused by the bacterium *Corynebacterium diphtheriae*. Characterized by grey, adherent, false membrane growing on mucous surface of the upper respiratory tract. Locally there is pain, swelling, and may be suffocation. Systemically the toxins attack the heart muscle and nerves.

DNA hybridization: Laboratory method for species and strain identification based on matching of DNA from an unknown organism with DNA from known organisms.

eastern equine encephalitis, abbr. EEE: An arbovirus disease of horses and mules, possibly other vertebrates, with a reservoir of infection in birds, transmitted by mosquitoes. Can be transmitted to humans and cause death. Occurring in the United States in a region extending from New Hampshire to Texas to Wisconsin, in Canada, Mexico, the Caribbean, and parts of Central and South America. Characterized by encephalomyelitis.

elephantiasis (el-ef-an-ti'a-sis): The swelling of a limb, usually a leg, as a result of lymphatic obstruction, followed by thickening of the skin and subcutaneous tissues. A complication of filariasis in tropical countries. See FILARIASIS.

encephalitis (en-sef-a-li'tis): Inflammation of the brain.

encephalomyelitis (en-sef'-al-o-mi-e-li'tis): Inflammation of the brain and spinal cord.

endemic (en-dem'ik): The constant presence or persistence of a human disease or infectious agent within a given geographic area. Cf. EPIDEMIC; ENZOOTIC.

enteric (en-ter'ik): Pertaining to the intestine.

entomology (en-to-mol'o-ji): The science dealing with insects.

enzootic (en-zo-ot'ik): The constant presence or persistence of an animal disease or infectious agent within a given geographic area. Cf. ENDEMIC; EPIZOOTIC.

epidemic (ep-i-dem'ik): The occurrence of a human illness in excess of usual frequency in a particular area. Cf. ENDEMIC; EPIZOOTIC.

epidemiology (ep-i-de-mi-ol'o-ji): The scientific study of the distribution and occurrence of diseases and health conditions.

epizootic (ep-i-zo-ot'ik): The occurrence of an animal disease in excess of usual frequency in a particular area. Cf. EPIDEMIC; ENZOOTIC.

Escherichia coli (esh-er-ik'i-a ko'li): A species of bacteria; motile, rod-shaped bacterium which is ubiquitous in the intestinal tract of vertebrates. Some strains are pathogenic to humans, causing intestinal disease and diarrhea.

etiology (ee-ti-ol'o-ji): The scientific study of disease causation; the causation of a disease.

filariasis (fil-a-ri'a-sis): Infection with Filaria, parasitic thread-like worms, found mainly in the tropics and subtropics, transmitted by mosquitoes. Adults of *Wuchereria bancrofti* and *Brugia malayi* live in the lymphatic system and connective tissues, where they may cause obstruction, but the embryos (microfilariae) migrate to the blood stream. Completion of the lifecycle is dependent on passage through a mosquito. See ELEPHANTIASIS.

genus (jen'us): The taxonomic category next greater than species.

granulomatous (gran-u-lom'ah-tus): Composed of tumor-like mass or nodule of tissue, due to inflammatory process associated with an infectious disease, such as tuberculosis.

helminth (hel'minth): Parasitic worm. Adj. helminthic.

hemorrhage: The escape of blood from a blood vessel.

hemorrhagic fever: Severe complication of some viral diseases involving internal or external bleeding.

host: Human or other living animal, including birds and arthropods, that affords subsistence or lodgment to an infectious agent under natural conditions.

human T-cell leukemia virus, abbr. HTLV: A recently identified virus that induces a specific type of cancer of the blood-forming organs.

immunity (i-myoo'ne-ti): Nonsusceptibility, or relative resistance, to a specific infection, due to antibodies produced against that specific antigen.

immunology (im'yoo-nol'o-ji): The scientific study of immunity. Adj., immunologic, immunological.

incidence (in'se-dens): The frequency of new occurrences of disease within a defined time interval. Incidence rate is the quotient of new cases of a specified disease divided by the number of people in a population in a defined period of time.

inflammation (in-flam-ma'shun): The reaction of living tissues to injury, infection, or irritation; characterized by pain, swelling, redness, and heat.

influenza (in-floo-en'za): An acute viral infection of the nasopharynx and upper respiratory tract.

in vitro (vi'tro): In glass, as in a test-tube.

in vivo (vi'vo): In living tissue.

isozyme (i'so-zime): Two or more forms of the same enzyme having identical chemical function but differing physical structure, which can be separated and identified.

isozyme electrophoresis (i'so-zime el-ek-tro-for-ee'sis): Laboratory method of separating isozymes (cf.) based on their migration distance in an electric field applied across a standardized inert material (polyacrylamide gel, agarose gel, or cellulose acetate).

jaundice (jawn'dis): A condition characterized by yellow appearance due to raised bilirubin level in the blood resulting from: 1) obstruction in the biliary tract, 2) excessive rupture of red blood cells, 3) toxic or infective damage of liver cells.

kwashiorkor (kwash-ee-or'kor): A nutritional disease produced by persistent deficiency in essential dietary protein. Characteristic features are anemia, wasting, edema, potbelly, depigmentation of the skin, loss of hair or change of hair color. Untreated, it progresses to death.

LaCrosse encephalitis: An acute encephalitis caused by an arbovirus, transmitted by mosquitoes. Closely related to California encephalitis.

Leishmania (leesh-may'ni-a): A genus of flagellated parasitic protozoans causing several clinical diseases. See LEISHMANIASIS.

leishmaniasis (leesh-man-i'a-sis): Infection by Leishmania, transmitted by sandflies. Cutaneous leishmaniasis is a skin ulcer caused by *L. mexicana* (New World) or *L. tropica* (Old World). Mucocutaneous leishmaniasis is an ulceration of the nose and throat caused by *L. braziliensis,* occurring in tropical America. Visceral leishmaniasis, also called kala-azar, is a generalized and internal disease caused by *L. donovani* (New and Old World).

leprosy (lep'ra-si): A chronic, infectious, granulomatous disease occurring almost exclusively in tropical and subtropical regions, caused by the bacillus *Mycobacterium leprae,* and ranging in severity from noncontagious and spontaneously remitting forms to contagious, malignant forms with progressive anesthesia, paralysis, ulceration, nutritive disturbances, gangrene, and mutilation. Also called "Hansen's disease."

leptospirosis (lep-to-spi-ro'sis): Disease caused by spirochete (finely coiled bacterium), commonly transmitted in water contaminated by urine of infected animals. Characterized by inflammation of the spinal cord, the nervous system, and liver.

lifecycle: The progressive stages of development of an organism.

lymphatic system (lim-fa'tik): The system of vessels in the body that carry lymph fluid.

lymph glands (limf-glanz): The organs at various points of the lymphatic system that filter the lymph fluid.

malaria: A disease caused by protozoan parasites that infect red blood cells, transmitted by mosquitoes of the genus Anopheles. Four species of the parasite cause disease in humans: *Plasmodium falciparum, P. vivax, P. malariae,* and *P. ovale. P. vivax* and *P. ovale* have a persistent stage in the liver that causes relapses. Many other species infect monkeys, rodents, birds, and reptiles. Characterized by fever, chills, and sweating that occur at intervals depending on the time required for development of a new generation of parasites in the body. See PLASMODIUM FALCIPARUM.

marasmus (ma-raz'mus): Wasting away of the body due to gross lack of calories in the diet.

measles (meez'lz): An acute infectious disease caused by a virus. Characterized by fever, a blotchy rash, and inflammation of mucous membranes.

metabolic: Pertaining to metabolism, the series of chemical changes in the living body by which life is maintained.

metastasize (me-tas'ta-syz): Tranfer of a disease from one part of the body to another, usually by blood or lymph, leading to secondary growth or lesions.

molluscicide (mol-lusk'i-side): Any chemical agent used to kill molluscs, especially snails.

morbidity: Disease or illness.

mortality: Death.

onchocerciasis (on-ko-ser-ki'a-sis): An infection of humans with Onchocerca worms, transmitted by the bite of blood-sucking blackflies (Simuliidae). Adult worms become encapsulated in subcutaneous nodules. Immature worms (microfilariae) migrate in the tissues and can cause "river blindness" if reaching the eye. Occurring in western Africa and discrete foci in tropical America.

oral rehydration therapy: The treatment of fluid-loss due to diarrhea by a specific water solution of electrolytes and glucose taken by mouth.

Oropouche fever (or-o-poosh): An arbovirus disease transmitted by biting midges (*Culicoides* spp.).

Characterized by fever, headache, aches and pains, and occasionally encephalitis. Found in Trinidad and Brazil, but recognized range in tropical America is expanding. Occurrence is primarily rural or forest, but explosive urban and suburban outbreaks occur.

parasitology (par-a-sit-ol'o-ji): The scientific study of parasites.

pathogen (path'o-jen): A disease-producing agent.

pathological: Of or pertaining to disease processes.

Phlebotomus (fle-bot'o-mus): A genus of sandflies, many of which are vectors of leishmaniasis. Adj. phlebotomine.

physiological: In accordance with natural processes and normal function of the body.

Plasmodium falciparum (plaz-mo'de-um fal-sip'arum): One of the four species of protozoan parasites causing malaria in humans. Only *P. falciparum* causes life-threatening complications; only species with drug-resistant characteristics. See MALARIA.

pneumoccocal (nyoo-mo-kok'al): Referring to the bacterium, *Diplococcus pneumoniae,* that causes pneumococcal pneumonia.

pneumonia (nyoo-mon'ya): Inflammation of the lung, usually the lower respiratory tract.

poliomyelitis (po'lee-o-my'a-li'tis): An infectious viral disease occurring mainly in children and in its acute, more virulent form attacking the central nervous system and producing paralysis, muscular atrophy, and often deformity. Transmitted by the oral-fecal route.

prevalence (prev'a-lens): The number of existing cases of a disease in a defined population at a particular time.

protozoa (pro-to-zo'a): Unicellular organisms, the smallest type of animal life. Adj. protozoan, protozoal.

protozoology (pro-to-zo-ol'o-ji): The scientific study of protozoa. Adj. protozoologic.

reduviid (re-du'vi-id): Belonging to the family Reduviidae, winged, "true" bugs (Order Hemiptera), including blood-sucking vectors of Chagas' disease. See CHAGAS' DISEASE.

reservoir: Any person, animal, arthropod, plant, soil or substance (or combination of these) in which an infectious agent normally lives and multiplies, on which it depends primarily for survival, and where it reproduces itself in such manner that it can be transmitted to a susceptible host.

rotavirus (ro-ta-vi-rus): Any of a group of viruses (round in shape) causing gastroenteritis in infants and children.

St. Louis encephalitis, abbr. SLE: An arbovirus disease transmitted by mosquitoes, with the reservoir of infection in birds. Can be transmitted to humans and cause death. First observed in Illinois in 1932. Occurring in most of the United States, Trinidad, Jamaica, Panama, and Brazil. Mild cases characterized by aseptic meningitis; severe infection usually marked by acute onset, headache, high fever, coma, convulsions, and paralysis.

schistosomiasis (shis'to-so-mi'a-sis): An infection of the human body by worms of the genus Schistosoma ("blood flukes"), from drinking or bathing in infected water. Infected humans pass eggs in urine or feces (depending on parasite species) into water source. Immature form (miricidia) hatchs and infects suitable snail host. After multiplication, intermediate form (cercariae) is shed from snail into water, where penetration of human skin occurs. Adult worm develops in human, localizing in veins of bladder or intestine. *Schistosoma mansoni occurs in Africa, the Caribbean, and Brazil; S. japonicum* occurs in the Far East; in both, adult worms localize in veins of intestine; deposited eggs cause tissue scarring of intestine and liver; *S. haematobium* occurs in Africa and the Middle East producing the urinary form as adult worms localize in veins of the bladder; characterized by obstruction due to scar formation, inflammation, and possibly cancer. Also called "bilharzia."

sequelae (se-kwel'ee): The pathological consequences of a disease.

seroepidemiologic: Pertaining to a branch of epidemiology that studies antigens from humans to delineate epidemiologic patterns of a disease. See EPIDEMIOLOGY; SEROLOGY.

serology (se-rol'o-ji): The scientific study of sera (the fluid portion of blood). Adj. serologic, serological.

sexually transmitted diseases: A group of infectious diseases defined by transmission through intimate contact, including gonorrhea, syphilis, chancroid, lymphogranuloma venereum, granuloma inguinale, chlamydia, herpes simplex, trichomonas, as well as hepatitis virus and intestinal parasites such as giardia, entamoeba, ascaris, and trichuris.

species: A taxonomic subdivision of a genus. A group of individuals having common characteristics distinguishing them from other categories of individuals of the same taxonomic level. Always carries the implication of reproductive isolation, i.e., members of a species only reproduce successfully with one another.

species complex: A group of two or more closely related insect species that can only be differentiated by cytogenetic analysis or cross-breeding experiments.

strain: A group of organisms of the same species (cf.) having a distinctive quality or characteristic (biochemical, pathogenic, or other feature) that can be differentiated, but not different enough to constitute a separate species.

subacute: Mild or moderately severe. Often the stage between the acute and chronic phases of disease.

symptomatic: Of or pertaining to the symptoms, rather than the causes of a disease.

symptomatology: The branch of medicine concerned with symptoms. The combined symptoms typical of a particular disease.

therapeutic: Dealing with the treatment of disease.

toxoplasmosis (toks-o-plas-mo'sis): Infection by the protozoal parasite *Toxoplasma gondii*. Many mammals can harbor the parasite which encysts in tissue after ingestion (oral-fecal route), but only in cats is the lifecycle completed, with the infective form shed in feces. Characterized by lesions of the central nervous system, which may lead to chorioretinitis, blindness, brain defects, and death.

trachoma (tra-ko'mah): A chronic, infectious disease of the eye caused by the bacterium *Chlamydia trachomatis*, characterized by inflammation, pain, watery eye, then scarring, and finally blindness.

triatomine (tri-a-to-meen): Pertaining to the genus Triatoma, blood-sucking bugs important as vectors of Chagas' disease. See CHAGAS' DISEASE.

trichuriasis (trik-u-ri'ah-sis): Infection with the intestinal parasitic whipworm, *Trichuris trichiura*.

Trypanosoma (tri-pan-o-so'ma): A genus of parasitic protozoans. Their lifecycle alternates between blood-sucking arthropods and vertebrate hosts. See TRYPANOSOMIASIS.

trypanosomiasis (tri-pan'a-so-my'a-sis): Disease produced by infection with Trypanosoma. In man this may be with *Trypanosoma cruzi*, transmitted by blood-sucking reduviid bugs in the Americas (also called Chagas' disease); or with *T. rhodesiense* in East Africa or *T. gambiense* in West Africa, both transmitted by the tsetse fly, causing "sleeping sickness." See CHAGAS' DISEASE.

tubercle bacillus (tu'ber-kl ba-sil'es): A bacillus causing tuberculosis; usually refers to *Mycobacterium tuberculosis*, the principal cause of human tuberculosis.

tuberculosis (tu-ber-ku-lo'sis): An infectious disease caused by any of several species of mycobacteria. Usually begins with lesions in the lung, but can metastasize to other parts of the body.

vector: A carrier of disease; usage commonly refers to arthropods or rodents.

vector bionomics: The relationship between organisms and their environment.

vector-borne: Transmitted by a vector.

vector control: Intervention aimed at disease reduction by action against vectors.

Venezuelan equine encephalitis, abbr. VEE: An arbovirus disease of horses and mules, possibly other vertebrates, with a reservoir of infection in birds, transmitted by mosquitoes. Can be transmitted to humans and cause death. Endemic in northern South America, Trinidad, Middle America, Mexico, and Florida. Characterized by severe headache, chills, fever, pain in muscles and eyes, nausea and vomiting, possibly with severe central nervous system complications leading to convulsions, coma, and death.

western equine encephalitis, abbr. WEE: An arbovirus disease of horses and mules, possibly other vertebrates, with a reservoir of infection in birds, transmitted by mosquitoes. Can be transmitted to humans and cause death. Occurring in Western and Central United States and Canada and in scattered areas further east. Characterized by encephalomyelitis.

whooping cough: Pertussis; an infectious respiratory disease of children with attacks of coughing which reach a peak of violence ending in an inspiratory whoop. Caused by *Bordetella pertussis*. Prophylactic vaccination is responsible for a decrease in case incidence.

yellow fever, abbr. YF: An acute febrile disease caused by an arbovirus, transmitted by mosquitoes. Characteristic features are fever, jaundice, black vomit, and anuria (absence of urine excretion). Jungle/sylvan yellow fever is maintained in monkey reservoir hosts; urban yellow fever refers to transmission with human reservoir hosts.

zoonosis (zo-on-o'sis): An infection or infectious disease transmissible under natural conditions from vertebrate animals to man.

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